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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

NOVEMBER, 1925

ORIGINAL ARTICLES.

THE BILIARY ASPECTS OF LIVER DISEASE.*

By Peyton Rous, M.D.,

NEW YORK.

(From the Rockefeller Institute for Medical Research.)

Were the project not a vain one, I would ask your indulgence to consider the state of our knowledge in case the biliary secretion, instead of the renal, was voided directly to the outside of the body. If, that is to say, the physicians of past times, whom we see in the Dutch pictures holding up a flask to the light, had had in that flask not urine, but bile. Knowledge would have been interestingly different. There would have accumulated a huge clinical pathology of the bile. For this secretion has its suppressions and its cholureses, its cylinders and desquamations, its pathologic albumin and other strange substances, as has the urine. But things are as they are; and until the specialist, with his little tubes, converts our inside into an outside, most doctors will have to be content with perceiving biliary disturbance at one or several removes.

Now, how small a biliary disturbance can the clinician perceive? Circumstances alter that case very much. The liver is the most silent of organs if only a moderate fraction of its cells are in a healthy state. The ducts from more than three-fourths of it can be abruptly obstructed, without causing even a ripple on the clinical surface of things.[1] Herringham[2] has collected a considerable number of cases in which, as a result of gradual obstruction of the left branch of the hepatic duct by a stone, the entire

* Read before the Association of American Physicians, May 5, 1925.

left lobe of the liver had atrophied. The patients in these cases never knew anything had happened to them. There was at no time any jaundice, and the condition was first recognized at autopsy. In such cases there had taken place, of course, a gradual compensatory hypertrophy of the portion of the hepatic tissue with unobstructed ducts. Liver cells have an astonishing ability to proliferate. After destruction of one-half of the hepatic tissue of dogs by chloroform, restoration may be complete within seven to nine days.[3]

The functional causes for biliary disturbance offer a far more complex problem than do mechanical ones. While the liver works extremely well, is a more than adequate mechanism, each cell being capable of doing at least four times the work in biliary excretion that it ordinarily performs, yet it is insensitive. It lets bile pigment slip past, never ridding the blood entirely thereof. It is, in fact, a threshold organ for this pigment, like the kidney; and there are natural and unnatural thresholds of bilirubin removal from the blood stream as in the renal instance. One may well believe that there is an unnaturally high threshold in congenital hemolytic jaundice and, perhaps, in pernicious anemia. During Frerich's time, sixty years ago, jaundice was frequently ascribed to functional causes that in the present day we would rule out of court. If a person had a fit of temper or another emotional shock he might turn up all yellow next day. With a more critical scrutiny of these cases they have disappeared. But one type of functional icterus, namely, that due to fasting, does remain. There can be no doubt that when the normal individual has been deprived of food for some hours bilirubin increases in his plasma. The state of affairs is subicteric, as in many other conditions. "Bilious" would be a better word, were it not in such bad repute.

You will note that by degrees I have come to talk of bilirubin and jaundice, not of biliary constituents generally. It is natural to think in terms of the bile pigment, for we know relatively little of the phenomena involving bile salts and cholesterol. Methods of quantitating these substances are difficult, and the results uncertain. Certain one can be, however, that the cholates play a far more important role, both normally and in disease, than does bilirubin, and that many more gall stones are formed out of cholesterol than out of bilirubinate. Bile salts are the substances responsible for most of the injury during biliary disturbances. They are, furthermore, a specific product of the hepatic parenchyma, whereas bilirubin is not. The amount of cholesterol in the bile can be greatly altered by the character of the food, as McMaster has proven definitely.[4]

It is customary to inquire, when one sees a case of jaundice, whether the coloration is obstructive or hemolytic in derivation. The distinction has clinical uses, though, of course, all jaundice

is blood derived. We now know, thanks to the work of Mann and his associates,[5] that the formation of bilirubin from hemoglobin is almost, if not quite wholly, extrahepatic. But the liver hallmarks the pigment as it puts it out,[6] with result that it can be recognized from that upon which the organ has not acted. There is a remarkably close relationship between current blood destruction and the intensity of a simple obstructive jaundice.[7] Under normal circumstances the variations in the amount of hemoglobin circulating as blood from day to day find a direct, if not entirely accurate, expression in the amount of bilirubin discharged into the bile. The corpuscular wastage would seem to be recorded almost immediately in terms of bilirubin; the greater the number of cell deaths the more the bilirubin put out. When obstruction is produced, most of the bile pigment formed is retained within the body, and, other things being equal, the jaundice that ensues will be more intense when the animal is full blooded than when it is anemic. If it is bled the jaundice diminishes very nearly in proportion to the amount of hemoglobin withdrawn, only increasing again as the loss of blood pigment is repaired.

The intercurrent variations in hemoglobin and bilirubinemia during uncomplicated obstructive jaundice accord with each other so closely from day to day that it is evident bile pigment cannot be readily distributed to the tissues, else they would take up the slack, so to speak, of the bilirubin accumulation in the plasma, and there would be little diurnal variation therein. To test the state of affairs is an easy matter. On collecting a specimen of lymph from the leg of a long jaundiced animal, one finds that it contains a negligible quantity of bilirubin as compared with plasma procured at the same time. Evidently there exists a barrier to the passage of bilirubin from the blood. Tissue icterus is in point of fact only the imperfect, secondary, expression of a condition primarily confined to the blood pool. Its intensity is, however, conditioned to no small extent by the tissue state. Schürer[8] and Jädassohn[9] have recently described a singular condition which the former terms "icteric skin writing." In their cases urticaria occurred, or was induced by artificial means, in patients that were jaundiced. The urticarial wheals were far more deeply pigmented than the surrounding tissue. In some instances this was due merely to the accumulation in the wheals of lymph colored like that elsewhere. But in others more pigment had come through locally from the blood stream, and there was plainly an increased permeability of the vessel walls to bilirubin. The question is worth proposing whether an increased permeability of the vessels may not have a share in the development of fulminant icterus.

If jaundice is fathered by the blood then certainly it is born of the liver. In asking whether it is hemolytic or obstructive, one is really asking, does the blood break down so fast that the liver

gets clogged secondarily, or is the liver so clogged to begin with that the products of normal blood destruction can find no outlet?

Pathologic disturbances affecting the ability of the liver cells to excrete bile pigment are a frequent cause of jaundice. The book written by Brulé[10] is instructive in this relation, and expresses well the French point of view as against that of a German school—the Germans are the metaphysicians of medicine—which would relegate all jaundice to mechanical causes. That there must be an icterus referable to cellular disturbances I believe most clinicians will agree. How else is one to explain dissociated jaundice, or the retention of two kinds of bilirubin, the so-called hemolytic and obstructive kinds? And how explain those cases in which, after operative drainage of the common duct, the bile, at first normal to all appearance, becomes lighter and lighter, though still copious, until finally a "white bile" is formed and the patient shortly dies with a greatly diseased liver?

It is simple to demonstrate the occurrence of jaundice from parenchymal disturbance by producing liver injury with chloroform.[11] As the injury develops the bile becomes progressively lighter and lighter, and shortly "white," while at the same time jaundice puts in an appearance. The secretion is not glairy, of the sort that would cause obstruction, but watery and clear. There are no changes within the hepatic tissue, such as would cause obstruction. It is probable that the partial or complete rejection of bile pigment by functionally damaged hepatic cells will explain many of the recorded instances of anomalous van den Bergh reactions.

There is another pigment, urobilin, which is important in relation to biliary disturbances. It is not an essential constituent of the bile, but is derived secondarily from the bilirubin of the secretion, and is hence directly dependent upon it. As a recent writer has stated, clinicians believe urobilin (under which name urobilinogen may be included) to be formed in the intestines by the action of bacteria, resorbed in part from the gut, carried to the liver by the portal circulation, and, under normal circumstances, removed therefrom by this organ. The clinical belief is correct, as the recent work of McMaster and Elman clearly shows.[12]

Their experiments have proved that the history of the pigment is as follows: It is formed in the intestine from bilirubin by bacterial action, is resorbed in part, and ordinarily the resorbed portion is so completely taken out of the blood by the liver that only a trace reaches the urine. Of the portion taken by the liver some, perhaps all, is excreted into the bile, and hence the normal bile regularly contains urobilin. If, now, bile be diverted from the intestine so that no bilirubin reaches the gut, to be worked upon there by bacteria, the diverted bile soon comes to be free from urobilin; while if bile is prevented from reaching the intestine by ligation of the common duct urobilin soon disappears from both feces and

urine. No matter how greatly one damage the liver of the animal with obstructed common duct, or with a fistula through which the bile is lost, the excreta remain free from urobilin. The same holds true even when a large part of the blood is broken down within the body by experimental means.

The liver has not so large a margin of safety for urobilin as it has for bilirubin. If one tie off only a small twig of the hepatic duct some of the urobilin absorbed from the gut passes through the injured portion of the liver and is excreted into the urine. As result of relatively slight hepatic injury one has urobilinuria, whereas a much larger one would not result in bilirubinuria.

It would seem, from what has thus far been said, that urobilin might be relied on as a highly useful sign of liver injury. Unfortunately there is more to the story of it. We have been considering what happens under conditions when there is no infection. But when the liver is infected, things may be very different. If one obstruct the common duct after infecting the bile in the passages with urobilin-producing organisms, urobilinuria will occur.[13] Many people have supposed that the liver cells themselves can form urobilin, but the evidence speaks conclusively against this. It is bacteria ensconced within infected ducts and perhaps within parenchyma, bacteria of a very special sort, which form the pigment out of bilirubin. To determine under what circumstances urobilin-producing organisms are found within the human liver will be an interesting task for the future.

Many of the bile constituents besides urobilin are resorbed in greater or less part from the intestine—bilirubin, cholesterol and, notably, the bile salts. The question may be asked, Is this resorption purposeful, brought about by a special arrangement? I do not believe that it is. Hinman[14] has shown that when the ureters are introduced into the small intestine by operative means, with result that all the urine is discharged into the gut, the animal resorbs the urinary constituents so completely as to die of uremia. It is probable that a similar process, incident to the physiologic activities of the mucosa of the gut, will suffice to explain the passage back into the organism of the bile constituents. Whipple[15] has trenchantly pointed out what would happen in case bile salts were quantitatively resorbed. With new salts being formed every day, and the old conserved through resorption, the patient would soon come to be, as he says, a pillar of bile salts. Granting all this, there can be no doubt that the body has adjusted itself to the resorption of biliary constituents so far as these influence its daily processes. Resorbed bile salts are known to stimulate bile secretion and for such reason are said to act as a "pace maker." In this relation it will not be amiss to point out that the bile obtained from a fistula animal is very different from the normal secretion. Owing to lack of the pace-maker influence the quantity secreted is greatly less than

normal. McMaster and Elman[16] have recently intubated small ducts from the liver, while allowing the greater part of the bile to flow to the intestine, and they find that the secretion collected from day to day under such circumstances is about three times as copious as that one would get from the same liver portion if all of the bile were being diverted from the gut.

Biliary disturbances mean disturbances of other functions as well as of the biliary function itself. On prolonged obstruction bile salts cease to be formed. Some substances which should be taken up by the liver and excreted into the bile are no longer so excreted. The hepatic cells form those curious little bodies known as bile thrombi which are not, as many have thought, inspissated bile, but a mixture of lipoids and protein, a product of damaged cells. The hepatic tissue does not take up hemoglobin with anything like the normal avidity. It does not lay down glycogen as well, and the quantity of sugar in the blood is increased. It does not form hippuric acid as well on test. In all these functions the organ obviously suffers, and in many others of which we know little. Yet it carries on remarkably well. I am speaking now of cases in which there is frank obstruction. When, by contrast, the liver parenchyma is at fault recovery or death takes place within a short period usually. Those cases in which one sees a long-standing icterus, with an excretion of bile still going on into the intestine, are cases in which the liver has been forced to the wall by repeated, localized injury, so that there has come to be less hepatic tissue than will suffice for the excretion of the daily quota of biliary constituents. This sort of thing happens at a late stage in Laennec's cirrhosis.

Recently there has been a productive revival of interest in the bile. Until it began our conception of biliary matters had been a masterpiece of the antique. Workers since Quincke had merely dusted off this masterpiece. But now, within a few years, much has come to be known. Clinical attention has been aroused, however, not by the new learning, but by the development of methods for quantitating the amount of bile in the blood, for obtaining bile from the duodenum and by the attempts to induce the gall bladder to discharge its contents. The question arises whether, when these technical advances have been perfected, and their limitations defined, clinical interest in the bile will flag? I do not believe it will, for the reason that workers are beginning to test liver function successfully. Not a few of the tests advocated are carried out with substances which find their way into the bile. In using these substances it is essential to know whether one is measuring liver function generally or merely biliary function. Before the point is settled much will inevitably be determined of biliary problems, and that is fortunate, because the bile is not merely an excretion—it is a highly purposeful secretion, and one susceptible to further utilization as an indicator of the liver state.

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RHEUMATIC FEVER.*

By Homer F. Swift, M.D.,
NEW YORK CITY.

(From the Hospital of the Rockefeller Institute for Medical Research, New York City.)

Three diseases causing very great economic loss are tuberculosis, syphilis, and rheumatic fever. Not only are the early acute stages of these maladies time-consuming in a period of life when the victims are of greatest value to the community, but their late manifestations, a consequence of their inherent chronicity, cause many individuals to be so severely crippled that they are often less efficient productive units.

About the first two, many positive facts are known; they have clinical, histo-pathological, and immunological points of similarity. Even though their respective causative agents occupy different positions in the biological scale, some of their manifestations are similar allergic expressions. In both we know the etiological agent: In one of them, syphilis, even though much had been learned empirically concerning the effect of mercury and iodids in an era of purely clinical study, the discovery of the Treponema pallidum led to important development in specific therapeutics. In the other, although the tubercle bacillus has been known for many years, no

* Trimble Lecture. Read before the Medical and Chirurgical Faculty of the State of Maryland, Baltimore, Md., April 29, 1925.

striking specific therapeutic measures have been derived from this knowledge. The information at our disposal, on the other hand, has led to important measures in the prevention of the disease; also, to a knowledge of the natural history of the tuberculous infection. The etiology of rheumatic fever is still undecided, hence we are forced to compare it with infections the nature of which are better understood.

We shall, therefore, draw attention to several points of similarity between these three diseases. I am assuming that rheumatic fever is an infection, with a great variety of manifestations; some short in duration and apparently inflicting but little damage on the tissues of the patient; others having a chronic persistent course from the onset with marked evidence of deep-seated injury to the affected organs; and still others in which there are alternate periods of activity and latency.

In making these comparisons it is possible to imagine ourselves in a period where the etiological agent in all three diseases was unknown. At that time many conditions were confused with tuberculosis: phthisis, consumption, often included diseases not due to the tubercle bacillus, although in the majority of instances this was the offending microörganism. Even now, the differential diagnosis in certain patients may rest, not upon the determination of the presence of the tubercle, but rather upon discovery of some other causative factor.

In such an attitude must we often approach our patients with rheumatic fever. It is not possible to be absolutely dogmatic about many cases. Some have symptoms that help in classifying them quickly; about others we are less certain. Doubtless numerous conditions other than rheumatic fever have been and still are included under the term rheumatism. The recognition of many forms of bacterial arthritis has helped to narrow the field so that there is less confusion in differentiating the various diseases with inflammation of the joints as their chief features. The characteristic response of some manifestations of rheumatic fever to certain drugs, such as salicylates, is also a diagnostic aid, just as iodids were formerly used in the differential diagnosis of syphilis. These differential diagnostic methods, however, merely help in bringing certain conditions into a narrower nosological zone; they do not offer much assistance in pointing to the true nature of the disease.

For this purpose we must not only study the manifestations of rheumatic fever directly, but must compare them with other conditions of an apparently similar nature and apply the positive information we have concerning the latter to the malady less well understood. But in making these comparisons it is well to keep constantly in mind that the diseases under consideration are not parallel in all respects. It is in the point of divergence that the peculiar picture of disease is brought out so that each infection has

more or less specific characteristics by which it is recognized as a separate entity. Thus the clinical manifestations of an infection are often determined because of the organs or tissues in which the virus is localized and the specific pathological responses occur. For example, in tuberculosis the lung seems to be most often involved because of its peculiar anatomical structure, and also because of a position favoring implantation of the tubercle bacillus. Similarly, in rheumatic fever the connective tissues in close apposition to large endothelial-lined body cavities or to synovial membranes seem to be especially predisposed to involvement. Nevertheless, if phthisis or scrofula were the only tuberculous manifestations recognized by us we would miss many important features of tuberculosis, so in the consideration of only arthritis and endocarditis we obtain an incomplete picture of rheumatic fever.

In the discussion concerning the relation of heredity and environment to the etiology of tuberculosis, and in the consideration of its contagious nature, the long periods of latency were very confusing factors; it is now well understood that five or ten years may elapse between the time of obvious opportunity of acquiring the infection and the appearance of symptoms. As Opie[9] remarks: "Tuberculosis has so few features of a contagious disease that its infectious nature was in dispute until Villemin's successful experimental inoculations and Koch's demonstration of the tubercle bacillus." It seems probable from clinical observation that similar periods of latency exist in cases of rheumatic fever and that comparable factors in heredity and environment play a role in the etiology of both diseases. For example, Cheedle[1] states that 70 per cent of his patients with rheumatic fever in private practice showed more than one case in the same family. Lately, St. Lawrence,[12] in a study of 100 families with rheumatic fever and 100 with tuberculosis in the St. Luke's Hospital Out-patient Department, showed that practically one-half the families in each group had 2 or more cases per family. There are also several important studies pointing to the possibility that house infections occur in rheumatic fever. It is, therefore, especially difficult to evaluate properly the relation of heredity, direct family infection, and house infection in the etiology of this disease. A recent report of Grenet[5] upon five distinct epidemics of rheumatic fever among Italian troops suggests strongly that direct infection from one person to another may take place and strengthens the opinion that the disease is due to a specific etiological agent.

In studying the various types of manifestations in patients of different ages we are struck by the fact that in both tuberculosis and rheumatic fever severe general acute manifestations are more frequent in the young than in the old. In succeeding decades of life there is a transition from generalized manifestations to more localized lesions. This we know in tuberculosis to point to the

development of an immunity or rather an allergy to the infectious agent. Perhaps a better example of this general principle is seen in syphilis where during the early secondary period there is a wide-spread dissemination of the Treponema pallidum and a generalized macular eruption. With each relapse these manifestations tend to become more and more localized and each individual lesion to be more deep seated and nodular. We now recognize this development of allergy to be an effort on the part of the body to restrict the activity of the virus to smaller and smaller areas. In tuberculosis this allergy is manifested in adults by a greater frequency of chronic tuberculosis of the lung. In rheumatic fever a similar tendency may be seen in the development of more frequent and severe joint lesions in adults than in children, possibly by a tendency to development of chronic arthritis. It does not require a great stretch of the imagination to picture the progressive thickening of the heart valves, the development of the mitral stenosis, the progressive increase of an aortic insufficiency, as sequelæ of the development of an allergy similar to that seen in tuberculosis. Sclerosis, the development of firm connective tissue from an inflammatory base, is a well-recognized feature of later periods of both diseases.

Let us return for a moment to an earlier age period, namely, that of childhood. Involvement of the central nervous system is seen relatively more often in the young than in adults. In children, tuberculosis often manifests itself as a generalized miliary tuberculosis, not infrequently, as a tuberculous meningitis. Similarly, chorea is a common manifestation of generalized rheumatic fever in the young. Accompanying tuberculous meningitis in a child we expect to discover other foci of infection in the lung or perhaps in all the viscera; similarly, in the presence of chorea we are not surprised to find cardiac lesions and frequently wide-spread subcutaneous fibroid nodules. In tuberculosis the severe manifestations usually lead to death; in rheumatic fever, the type of infection, being less severe, leads to a chronic disease which most often expresses itself as a persistent carditis.

A variation in the susceptibility of various systems of the body at different ages has already been suggested. These systems need not necessarily all be simultaneously involved. In other words, if the virus be generally disseminated, all of the organs do not necessarily respond to this invasion at the same time. For example, although we usually see in children extensive evidence of involvement of the various structures, the child at one time may have chorea, a little later subcutaneous nodules, and still later evidence of marked cardiac disease. The order of involvement does not necessarily follow that given above. In fact, we have examples of nodules with cardiac symptoms, or nodules alone and later chorea. Only one type of manifestation may be detected for a long time; and this fact supports the conception that chorea or

subcutaneous nodules occurring in the absence of any other symptoms are really rheumatic in nature.

The tendency for a person to have several attacks of rheumatic fever has long been known. Two points of view regarding this phenomenon are possible; the first is that he is susceptible to the peculiar type of infection and that each attack is the result of reinfection in the same manner as we regard several attacks of lobar pneumonia in one individual as due to different types of pneumococci. The second conception is that the various acute attacks are evidences of relapses of an infection having alternate periods of latency and activity. This view predicates that the patient is infected but once and that clinical recovery is due to the development of a partial immunity resulting in an incomplete elimination of the infectious agent from the body; later some depressing influence lowers the patient's resistance and the dormant virus again becomes active. The well-known chronicity of rheumatic fever in children is good evidence of the capacity of the infectious agent to persist in the body; and it is not rare to encounter similar examples in adults.

All grades of transition between these very chronic cases and those showing rapid and apparently complete recovery without the intervention of drugs are seen. Not infrequently one meets patients with the signs of chronic infection in evidence for many months, in whom finally the inflammatory process seems to have come to an end; in other words, the patients even with marked cardiac disease have apparently overcome the infection. I use the word "apparently" because experience has taught us to assume the same attitude toward recovery as those responsible for the care of tuberculous patients take in using the term "arrested." In both instances the physician is prepared to see at any time a reawakening of activity.

Unfortunately the etiological agent of rheumatic fever has not been demonstrated conclusively; nor has it been possible to reproduce in animals the characteristic clinical or histo-pathological picture of this disease. This may be due to the absence of the causative agent in the material injected or to the failure of the lower animals to react in the same manner as man to the same irritating substance. Many consider the disease to be due to the so-called Streptococcus rheumaticus, which is really the nonhemolytic streptococcus; but I do not think this opinion can be unqualifiedly accepted. The endocardial vegetations and myocardial lesions so characteristic of the disease known as subacute bacterial endocarditis are also seen in animals properly inoculated with streptococcus viridans. The characteristic microscopic lesions of rheumatic fever, namely, Aschoff bodies are not found in the hearts of either these patients or animals. How then are we to regard the occasional recovery of nonhemolytic streptococci from the blood or gross lesions of patients with rheumatic fever? Up to the present we[6] have been unable to

place the strains so recovered in any small number of biochemical or immunological classes such as has been done with the pneumococcus, streptococcus scarlatinæ, or streptococcus erysipelatis. Furthermore, we have been unable to demonstrate in the serum of any rheumatic fever patient a specific agglutinin or precipitin against the homologous streptococcus previously recovered from his blood or lesions. We[15] have been able to demonstrate complement binding antibodies against the nucleoproteins of streptococci, both green and hemolytic, but could find similar antibodies in the serum of convalescent pneumonia patients and in apparently normal individuals. R. C. Lancefield,[7] in our laboratory, has shown that this cross fixation is probably due to the immunological similarity of nucleoproteins of hemolytic streptococci, nonhemolytic streptococci, pneumococci, and, to a smaller extent, of staphylococci. It is, therefore, impossible to use positive results obtained in complement-fixation tests with antigens containing nucleoproteins of streptococci as conclusive proof that they are the etiological agents; in other words, it is difficult, if not impossible, to use the complement-fixation reaction to detect specific infections with hemolytic and green steptococci. Nevertheless, recent interesting and important studies concerning the nature of streptococcus infections indicate how necessary it is to maintain an open mind as to the relationship between these microörganisms and rheumatic fever.

In the absence of a specific etiological agent or of an immune reaction to give us an indication of uniformity of this disease we are forced to search elsewhere for this clue. Histo-pathology in this respect has furnished us with valuable information in more than one disease. For example, in syphilis the perivascular granuloma is the general type of response to the irritating action of the Treponema pallidum. Straus[13] has defined tuberculosis as a general disease characterized by miliary eruptions in various organs. One might paraphrase this definition in describing rheumatic fever as a general infection characterized by submiliary nodules in certain organs. In the rheumatic heart as already mentioned this nodule has its most characteristic appearance as the Aschoff body; it may be interpreted as a focal interstitial inflammation, situated in the tissue around the smaller arteries and arterioles; there is both a stimulation of fixed cells somewhat similar to the endothelioid cells of the tubercle and an invasion of wandering cells. The peculiarity of the lesion is the presence of "irritation cells"—giant cells of a different type than those seen in the tubercle. There is practically always necrosis of the center of the nodules as well as of the contiguous muscle fibers. The healing of the lesion is attended with scar formation.

While the picture of the Aschoff body is not completely reproduced in the other focal lesions of rheumatic fever, the differences can be largely explained upon differences in the tissue involved and the presence of a superimposed exudative process. In the mural

endocardium nodules identical in appearance have been found; their presence in great numbers in the left auricle has recently been shown by MacCallum[8] to give a peculiar gross appearance to the lining structures. It seems to us that essentially the same process is responsible for the valvular changes. In most descriptions of rheumatic endocarditis the chief stress is laid upon the very obvious verrucæ; but careful microscopic examination of the entire valve practically never fails to reveal important interstitial changes occurring throughout the major portion of the leaflets. The existence of blood vessels and of areas of inflammation in long-standing rheumatic valvulitis is well recognized and has been explained as secondary to the injury of the endocardium and formation of verrucæ. This conception predicates that the initial injury of the valve is due to the deposition of the causative agent in the cells of the valvular endothelium, then a death of the contiguous structures, followed by a deposition of the various thrombotic elements from the blood stream to form the verrucæ. Recently we have had the opportunity of examining the tissue from 4 patients dying of this disease within two or two and a half weeks of the appearance of the arthritis; in 3 the attack was the first one noted by the patient; in the fourth it was the second. In the first no verrucæ were detectable macroscopically, but many typical submiliary nodules were found in the valves and adjacent chordæ; numerous areas of perivascular inflammation were present throughout a thickened valve; and occasionally definite endarteritis was discernible in the smaller vessels. The entire valve was swollen; but only in one small area of the endocardium was there evidence of necrosis and early verruca formation. The second case showed similar vascular changes and areas of focal inflammation throughout the valvular tissue, a few typical submiliary nodules and slightly larger flat verruca formation in one small area. In the third patient the fatal issue occurred during tonsillectomy on the nineteenth day when it was felt that he had entirely recovered from the acute disease. A small verruca was found at only one place on the aortic valve, but in the substance of the valve there was distinct evidence of mild interstitial inflammation. The death of the fourth patient occurred on the fourteenth day of the second attack of the disease. Grossly no vegetations were seen on any of the valves, but microscopically there were present many foci of intense infiltration with polymorphonuclears, lymphocytes and a few large endothelioid cells. In a few small areas there was desquamation of the valvular endothelium and very slight deposit of fibrin which was interpreted as early evidence of verruca formation.

From the clinical study of rheumatic polyarthritis we know that swelling due to the exudation of edema fluid and wandering cells can be a marked feature of the inflammatory response. In the valves above described there was also evidence of a similar swelling.

It seems to us, therefore, that the primary reaction in rheumatic disease of the valves is in the interstitial tissue, and that the verrucæ are usually due to the deposition of thrombi on a portion of the valve where the vitality of the endothelial and subendothelial layers of the endocardium has been impaired as a result of repeated impacts with the contiguous valve. This theory of death of the endocardium being due to mechanical trauma of an already inflamed structure offers a rational explanation of the localization of the vegetations at a distance from the free margin of the valve. It is also possible that single small verrucæ might form at a point where a submiliary nodule broke through the endocardium. Cary Coombs[3] has marshalled convincing evidence that interstitial valvulitis is the important feature of rheumatic endocarditis.

The recent extensive investigation of Pappenheimer and Von Glahn[10] indicates that essentially the same type of response is ordinarily present in the aorta of patients dying as a result of rheumatic carditis. Upon first glance it might seem that pericarditis was an entirely different process; but in inflammations of this structure the outpouring of serum and fibrin is the usual response to injury whether this be due to the tubercle bacillus or to the causative agent of rheumatic fever. The thick layers of fibrin and subsequent organization may mask the primary lesion; but we have found in the pericardium bodies closely resembling Aschoff bodies, and in the fibrous tissues of adherent pericardiums active perivascular focal reactions closely resembling those found in sclerotic valves.

In the subcutaneous fibroid nodules we have lesions grossly more comparable with tubercles. When excised early they have a similar yellowish gelatinous appearance. Microscopically they are seen to consist of central areas of necrosis containing a small amount of fibrin; surrounding this there are perivascular collections of many large polygonal and branching cells with basophilic protoplasm, lymphocytes, and polymorphonuclear leukocytes in varying numbers. In subcutaneous nodules removed soon after their appearance I[14] have seen polynuclear cells closely resembling the "irritation giant cells" of the Aschoff bodies. Large subcutaneous nodules may be considered as conglomerations of many small submiliary nodules. Poynton and Holmes[11] describe perivascular submiliary nodules in the brains of patients dying from chorea. The most rational explanation of the symptoms of chorea is the presence of focal areas of encephalitis. At times the meninges may be involved; but encephalitis may occur without meningitis just as myocarditis may occur without pericarditis.

The response of the tissues about the joints to the virus of rheumatic fever is now known to be essentially the same as that found elsewhere. Both Coombs[2] and Fahr[4] have described focal proliferative inflammation in periarticular tissues obtained postmortem from subjects dying from rheumatic heart disease. Recently we[14]

have excised bits of joint tissue from patients during the first week of an acute attack and found vascular and perivascular lesions in every respect similar to those present in subcutaneous nodules. When the patient had received no antirheumatic drugs there was, in addition, marked edema of the tissues; when he was fully under the influence of salicylates the exudative features were less prominent, but submiliary proliferative lesions were still easily found.

Combined clinical and histo-pathological studies have, therefore, taught us that there are two general types of response on the part of the body to the invasion of the causative agent of this disease, namely, proliferative and exudative. At the bedside the only visible proliferative lesion is the subcutaneous nodule; but the interpretation of many symptoms and signs as well as of the peculiar course of the disease is made simpler by the knowledge that comparable changes are occurring in important organs. The exudative response, on the other hand, is more evident in the swelling, pain, and tenderness seen in acute rheumatic polyarthritis. Probably the most characteristic feature of this disease is the disappearance of exudation and the symptoms dependent upon it following the exhibition of sufficient doses of certain drugs. It is well established, nevertheless, that subcutaneous nodules may appear continuously in a patient who is receiving maximum doses of salicylates. The failure of the salicylates to influence markedly the proliferative lesion probably explains why the symptoms of chorea persist and the development of valvular disease continues in patients who are receiving apparently full therapeutic doses of salicylates or neocinchophen.

It may be well to mention certain other peculiarities attending the two types of response; at the same time keeping in mind that usually there are combinations of the two, and that the clinical picture is dependent upon which one predominates. With acute toxic symptoms and high fever one expects to encounter exudative manifestations; as the course becomes chronic the fever is lower and symptoms depending upon the existence of proliferative tissue alterations in the involved organs become increasingly predominant. There are, moreover, cases in which a low grade, chronic course is always the outstanding feature. Doubtless many patients with this type of infection never come under the care of the physician until they have marked cardiac disease. It has been brought to our attention that in many parts of the world there seems to be almost a complete absence of acute articular rheumatism and still mitral stenosis is not infrequent. If we regard this form of valvular disease as practically always of rheumatic origin we may assume that the disease as it exists in those localities assumes a chronic proliferative course from the beginning, either due to the fact that the etiological agent in those regions is more attenuated in character or that the persons affected have an inherently different type of immunity.

It is possible that a changing character of the infection explains the diminution in the frequency of the condition known as acute inflammatory rheumatism; but in this respect it must be borne in mind that the use of salicylates is one of the most common of practices. Indeed, it is almost necessary to write a new clinical description of the disease with the patient under the influence of partial or complete therapeutic doses of the various antirheumatic drugs. A study of the older literature makes it evident that in most instances the infection is self limiting: at times after two weeks, at other times after two, or three months, and in many instances after longer periods. If a patient is kept under the influence of salicylates the obvious clinical manifestations of recurring or continuing infection are often masked. It is necessary, therefore, to document more carefully the slight symptoms that persist, and to resort to more careful instrumental examination of the patient to detect signs that would otherwise escape our notice. Thus we have found that curves of leukocyte counts made at weekly intervals in most cases serve as a fair index of the persistence of infection. It is true that in some patients there were other evidences of active disease even in the presence of repeated normal leukocyte counts; and rarely in others abnormally high counts have persisted in spite of the absence of other evidences of persisting infection. As clinicians, we should recognize the necessity of properly evaluating symptoms and signs and should not disregard certain ones because in some exceptional instances they have not followed the accepted rule.

COMPARISON OF ELECTROCARDIOGRAPHIC EVIDENCE OF MYOCARDIAL DISTURBANCE WITH AUSCULTATORY EVIDENCE OF VALVULAR DISEASE AND PERICARDITIS IN 81 CASES OF RHEUMATIC FEVER.

	Total cases.	Increase in *P–R* time.				Change in form of electrocardiogram.	Valvular disease.				Pericarditis.
		Number.	With fever.	Without fever.	Incomplete heart block		None.	Doubtful.	Mitral.	Aortic.	
First attack . .	34	29	22	21	4	33	5	12	16	5	6
Recurring attacks	34	30	24	13	2	29	1	5	28	8	3
Cardiac type .	13	11	10	4	4	13	..	..	13	(8?) 7 (4?)	7
Total . . .	81	70	56	38	10	75	6	17	57	24	16
Per cent . .	..	*87*	*69*	*47*	*12*	*93*	*7*	*21*	*70*	*30*	*20*
							28				

Practically all statistics of the relative frequency of involvement of the heart in rheumatic fever rest upon the occurrence of murmurs which the examiner interpreted as due to deformities of the valves. Pericarditis, obviously, is an indication of very severe cardiac injury. Study of the heart's action with the electrocardiograph has furnished us with evidence that there is some degree of functional disturbance in over 90 per cent of patients suffering from this disease (see Table). While it is impossible to be absolutely certain that these electrocardiographic alterations are caused by structural changes in the heart, and it has been shown that the administration of digitalis, ether, and histamine may produce similar alterations in the electrocardiogram, our knowledge of the histo-pathology of rheumatic myocarditis permits us to assume with a fair degree of assurance that these abnormal electrocardiograms are the result of some injury to heart muscle or conduction system. It should be pointed out that these unusual curves in many instances have been only transitory and that upon recovery from the acute infection the form of the curve and the function of the heart have returned to normal and remained in that condition for many years. It may be that changes in conduction time or in form of the ventricular complex are caused by a transitory edema about a few submiliary foci which of themselves are relatively unimportant. A very valuable conclusion to be drawn from this type of evidence, however, is that the heart is probably affected to some degree in practically every patient suffering from rheumatic fever. This conception should eventually alter our attitude toward the therapeutics of this disease.

Other indications of myocardial implication during the period of acute infection are transitory precordial pain and hyperesthesia, and the occurrence of abnormal rhythms; among these the most common is gallop, apparently caused by a marked exaggeration of the normal third heart sound. We have noted repeatedly that such gallops were accompanied by distinct alterations in the form of the electrocardiogram. The interpretation of the murmurs so frequently heard during this disease must often await the results of observations extending over months. The point to be especially emphasized is that a search for murmurs is only one of a number of examinations it is necessary to make in order to detect evidence of cardiac derangement.

It has long been recognized that an impaired nutritional state was a feature of the rheumatic infection. Clinical descriptions made in the presalicyl era indicate that marked emaciation was frequently seen in those patients with the subacute and chronic form of the disease. One distinct benefit from antirheumatic drugs is that with the control of the fever and its concomitant toxic state the tendency for the patient to lose weight is less marked. The weight curve, nevertheless, is still a good auxiliary guide in helping us to determine whether or not the patient is succeeding in overcoming

his infection. Not infrequently one notes a continual loss in weight when other symptoms seem to be fairly well controlled by salicylates; also relapses are often heralded by declining weight. There is a more or less common, but unfounded belief that errors in diet or metabolism are important etiological factors in rheumatic fever. These opinions arose from the lactic acid theory of rheumatism, from confusion with gout, and lately from the hypothesis that arthritis is due to a high blood sugar. As a result of these opinions has arisen the practice of omitting fruit to eliminate certain organic acids, red meat "to combat uric acid," and reducing carbohydrates to lower blood sugar. As a result of this régime many of the patients suffer from undernutrition with a consequent deleterious influence on their natural powers of resistance.

Assisting a patient to overcome his infection by increasing his general nutrition has been shown to be one of the most important therapeutic measures in tuberculosis. Maintaining or increasing a typhoid fever patient's weight has been shown to shorten the period of convalescence from that disease. In our experience the maintenance of nutrition is one of the most important therapeutic measures for rheumatic fever.

Analysis of a large series of charts of rheumatic fever patients, in which have been documented all of the signs and symptoms as well as the various laboratory records of activity of infection, has convinced us that the drugs we have been considering as specifics are probably antisymptomatic in their action; and that if patients are carefully studied while under their influence not infrequently signs of persisting infection will be discovered. By means of salicylates or neocinchophen, distressing symptoms of arthritis are fairly easily controlled and high fever is eliminated with a corresponding reduction of the pulse rate. This doubtless spares the heart in more than one respect. If edema is eliminated from the valves by the drugs in the same manner as from the periarticular tissues it is conceivable that the endocardium might be spared some of the traumatic injury to which we think a swollen valve especially liable. A 20 or 30 per cent reduction of the heart rate reduces the number of impacts of the injured valve by a corresponding amount.

All of these are desirable aims of therapeusis; but if in attaining them the patient is led to believe that he is cured of his infection, or the physician is blinded to the pathological processes that are persisting in spite of the absence of obvious symptoms, the patient may in the end suffer as much permanent injury to some important organ as if he had passed untreated through an attack of the disease. Probably most physicians can remember many patients who have been allowed to be up and about in the wards or in their homes while under the influence of therapeutic doses of salicylates or neocinchophen, and who had relapses when these drugs were discontinued. A common practice is to discharge from the hospital patients while

under the influence of these drugs. The reason for this is obvious. The physician often believes that the elimination of symptoms by salicylates is a sign of eradication of the disease; and in a desire to turn over the service as rapidly as possible the doctor yields to the importuning of an apparently well person to return to his home. We may profitably revert to our comparison of syphilis and rheumatic fever in their response to certain drugs. The disappearance of gummata following the administration of iodids was not a sign of the elimination of the treponema from the patient; nevertheless iodids have an important place in the treatment of a patient with syphilis and often help in saving an important organ from irreparable damage. Other therapeutic measures must, however, be applied if the patient is to be cured. Similarly in the treatment of rheumatic fever the beneficial effects of salicylates must be complemented by other measures which have been shown to be of benefit in combating infection.

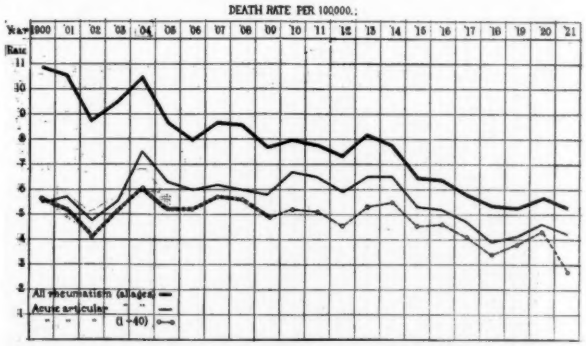

CHART I.—Death rate from all rheumatism, and from acute rheumatic fever in New York State, 1900–1921.

At this point it may be asked what have been the influences of our drug therapy upon the development of chronic cardiac disease, as well as upon the death rate from rheumatic fever itself. Both the impressions of physicians and vital statistics seem to indicate that the death rate from rheumatic fever is less than in former years (see Chart I). Death during the acute stages of rheumatic fever is usually due to one of three causes: Hyperpyrexia, severe general intoxication, and acute heart failure resulting from severe myocarditis. Doubtless the use of the drugs at our disposal has been instrumental in eliminating to a large extent the first two of these lethal complications. The lower death rate may be due, therefore, in part to a decreased incidence of rheumatic fever as a result of the application of general hygienic measures and also to better treatment during the acute stages with a consequent result that the condition is one that is recorded as cardiac disease instead of rheumatic fever.

The failure of health departments to make rheumatic fever reportable leaves us without any source of information as to whether or not there is a decreased incidence of this disease. Likewise our ideas as to trends in the incidence of heart disease must be based upon mortality rates. In the Registration Area of the United States, vital statistics show that deaths from cardiac disease of the entire population is steadily increasing; but these trends can be explained to a certain degree by the fact that as the expectation of life increases there is more opportunity for the degenerative cardiovascular conditions to be an increasingly important factor in the death rate. If we are to obtain an approximate idea of the trends in rheumatic

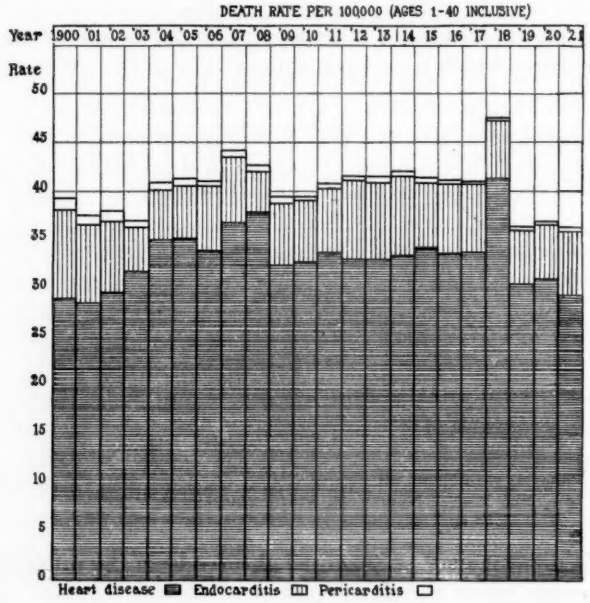

CHART II.—Specific death rates (ages one to forty years inclusive) for heart disease, endocarditis and pericarditis in New York State, 1900–1921.

heart disease we must select age periods when we think the rheumatic infection is the most active. Analysis of the deaths from heart disease, endocarditis and pericarditis in New York State from the years 1900 to 1921 show practically no diminution in the rate of this period (see Chart II). Certain distinct cycles are noted with more deaths in the years of influenza epidemics followed by a decrease in the two or three subsequent years, and then a slowly rising rate until the next epidemic. Life insurance data indicate an increasing rate since 1921. Comparison of the death rates from heart disease and pulmonary tuberculosis in NewYork City in the past six years, shows that in children of school age, heart disease is

now three times more frequently a cause of death than pulmonary tuberculosis, and that in later age groups with the fall in tuberculosis death rates, there is a slight but steady increase in deaths from heart disease. Insofar as vital statistics are of value in judging the effect of our therapeutics, it seems that both the preventative and curative measures so far applied to infectious heart disease have been of little value.

We may well inquire the reasons for this failure, and ask whether conditions may be remedied.

Successful prevention of an infection depends primarily upon a knowledge of the nature of the etiological agent, how it enters the body, where it increases in the body and whence it emerges from the body. Attention has already been drawn to our ignorance of most

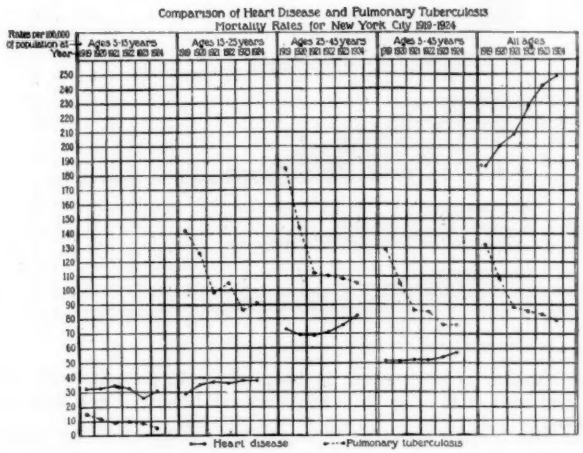

CHART III.—Comparison of death rates from heart disease and pulmonary tuberculosis for certain age groups in New York City, 1919–1924.

of these factors in regard to rheumatic fever. Protective immunization depends upon our ability to manipulate the etiological agent successfully. Chemotherapeutics as applied to prevention of a disease must be founded upon positive demonstration that the drug applied is effective in reaching and destroying the etiological agent and not simply in alleviating symptoms. The successful warfare against tuberculosis has been based not only upon the destruction of the tubercle bacillus in the material in which it was excreted from the body, but also upon a recognition of the chronic nature of the infection and the application of suitable measures to enable the patient to combat that type of infection.

This brings us directly to what I regard as probably the most important phase of treatment of rheumatic fever, namely, the length of time it is necessary to keep the patient quiet. Briefly, it

can be stated that this should be as long as signs of infection persist. Recognition of the different types of the disease already mentioned and the determination into which of these types a patient falls is most useful; for it is obviously unwise to keep a patient with a short course of rheumatic fever in bed a long period, and conversely permitting a patient with a drug masked active infection to be up and about is not the best measure to conserve his strength, protect his heart, and increase his powers of resistance.

The period of rest needed is longer than is usually recognized or enforced. A summary of the length of time it was necessary to keep 72 of our patients in the Rockefeller Hospital is shown in Chart IV.

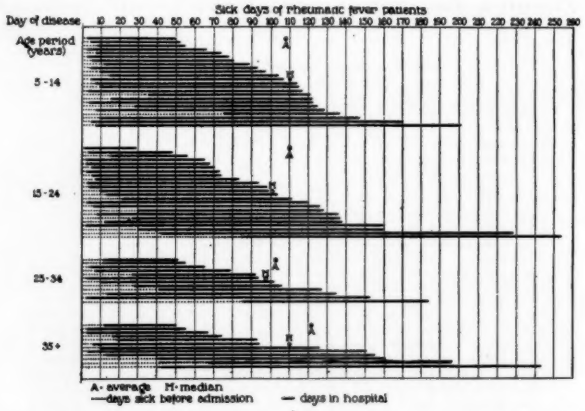

CHART IV.—Number of days spent in hospital by 72 patients with rheumatic fever, before they were able to go to a convalescent home. Each line represents time of 1 patient.

This period was only that spent in hospital and does not include an average of from two to six weeks in a convalescent home after leaving the hospital.

Let us make clear that these patients were treated according to the accepted methods, that is, antirheumatic drugs for arthritis and high fever, removal of such diseased foci as tonsils and teeth, and treatment of sinuses or other possible infected foci. Our special care was to keep patients quiet until signs of active infection had passed.

If general hospitals kept their patients with rheumatic fever for periods similar to this there would be none other than rheumatic fever patients in the wards during the winter and spring months. The question to be met is: "How can these patients be given proper periods of rest?" In this one point of proper provision for rest cure the institutional and sanatorium treatment of tuberculosis has pointed a way. Perhaps the time may come when the tuberculosis problem has been completely solved and these sanatoria will

be converted into hospitals for the treatment of patients with rheumatic hearts; but before that time it is to be hoped that provision for the proper care of a large group of these patients will have been made. A few heart hospitals where proper study of these problems could be both intensively and extensively carried out would do much toward formulating a definite plan in the treatment of a condition which up to the present has been but little permanently benefited by the methods now in vogue.

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CLINICAL OBSERVATIONS ON THE VALUE OF CALCIUM CHLORID AS A DIURETIC AND ON ITS INFLUENCE UPON THE CIRCULATORY MECHANISM.

(Seventeen Cases of Cardiac Failure, One of Tuberculous Effusions in Serous Cavities, One of Hepatic Cirrhosis with Ascites and Two Normal Controls.)

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Literature. In 1918 Schutz reported beneficial results from large doses of calcium chlorid administered by mouth in cases of war

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nephritis with edema. In a number of his cases this therapy alone did not cause diuresis, but on the addition of digitalis a marked diuresis resulted with the reduction of edema. He inferred from these observations that calcium chlorid did not affect the cardiac factor in the etiology of edema in these cases.

On the other hand, Singer in 1921 found that the intravenous injection of calcium chlorid (0.5 gm.) or the oral administration of calcium lactate (3 gm. per day) caused a temporary diuresis in cases of cardiac failure as well as in so-called cardiorenal cases with edema. He observed that these calcium salts also caused temporary strengthening of the heart action, slowing of the heart rate and lowering of blood pressure. He also states that the best results are obtained by giving these calcium salts and digitalis simultaneously. Cheinisse also reports that calcium chlorid given intravenously in doses of 1 cc. of a 10 per cent solution is a good adjuvant to digitalis in cases of cardiac failure with edema.

More recently, Walters and Bowler investigated the effect of intravenous injection of calcium upon the heart experimentally in normal and jaundiced dogs. They found that therapeutic doses (82.5 mg. per kilogram of body weight injected in a 10 per cent solution at the rate of 1 cc. per minute) quickened the pulse somewhat but they did not find any change in blood pressure even during gradual increase of the dose to the lethal amount by the gradual injection of the 10 per cent solution at the rate of 1 cc. per minute. Lethal doses caused tachycardia, ectopic origin of impulses, disturbances in conduction and finally ventricular fibrillation followed by death of the animal. They refer to the occurrence of tachycardia and the sensation of flushing of heat all over the body in patients during the intravenous administration of calcium chlorid. However, with Hirschsohn and Maendl, they attribute these phenomena to the "dynamic effect" of intravenous injection *per se*, for similar phenomena have been observed following the injection of solutions of quinin, dextrose, hexamethylenetetramin and urea. It is probable that the observations made by Singer correspond to this temporary reaction.

Blum and his collaborators have reported results which indicate that calcium chlorid is an effective diuretic and causes elimination of fluid from serous cavities in cases of inflammatory effusions in the pleural sacs or in cases of hepatic cirrhosis with ascites. Krummenacher and others have reported similar results. Blum and his collaborators, however, sounded a warning against the use of calcium chlorid administered by mouth in cases of edema of cardiac failure, since in their experience the condition of such patients became aggravated as a result of this therapy.

Lowenberg recently reported investigations which led him to conclude that in small doses of 0.1 to 1 gm. calcium chlorid has a cardiotonic but no diuretic action, whereas this latter effect takes

place only after the administration of doses larger than 1.5 gm. From these premises he infers that the diuresis caused by calcium chlorid is not due to its cardiotonic influence.

In 1920 Denis and Minot drew attention to the fact that the upper level of calcium content of blood serum tends to be fixed and could be raised for but a very short period of time (if at all) by the ingestion of large quantities of calcium chlorid. Their observations have been repeatedly corroborated by other investigators. It would seem, therefore, that a continued diuretic effect during and after calcium chlorid administration by mouth is not the result of increased calcium content of the blood.

In 1911 Meyer and Cohn showed that the oral administration of calcium salts to normal infants causes decrease in weight due to loss of water from the body. These investigators found that the calcium ion is excreted mainly in the stool, that the chlorin ion combines with other bases and that the resulting chlorids are excreted in the urine. More recently, Jansen has shown that even after intravenous injection of various calcium salts, including calcium chlorid, the calcium ion is largely excreted in the stool.

In 1921 Vlum and his colleagues found that with the administration of calcium salts, when no diuresis occurred, sodium was retained, while during diuresis an increase in sodium excretion was found. This they attributed to the antagonistic action between the calcium and sodium ions. They therefore advocated the use of salt-free diet together with calcium chlorid in the treatment of nephritis with edema.

Atchley, Loeb and Benedict studied a case of diabetic coma with edema treated by the oral administration of large doses of calcium chlorid per day, and observed a marked diuresis which began at the end of the first twenty-four hours of this therapy. They found the chlorin ion was excreted largely in the form of ammonium chlorid, while sodium excretion was also increased. They compared the data in this case with the data in a case of diabetes with spontaneous diuresis and found no essential difference. They also studied the effect of 20 gm. of calcium chlorid given by mouth to a normal individual; in this case marked diuresis occurred and they found an increase in the amount of sodium, chlorin, potassium and ammonia excretions.

Haldane, Hill and Luck also found increased ammonium chlorid excretion following the ingestion of large doses of calcium chlorid by a normal person. They believe that the diuresis may be due to lowering of osmotic pressure in the tissues, which is caused by disturbance of the Donnan equilibrium as a result of the slight acidosis developed during the ingestion of large doses of calcium chlorid. Gamble, Ross and Tisdall offer a similar explanation for the diuresis which results from the administration of hydrochloric acid, ammonium chlorid and calcium chlorid. Most recently, however,

Salvesen, Hastings and McIntosh have reviewed the subject of the effect of calcium salts on the inorganic composition of the blood, and from their work as well as from that of others they conclude that the question whether the diuretic effect of calcium salts is dependent on the anion and is in some way connected with the production of acidosis is as yet unsettled.

Rockwood and Barrier report 7 cases of edema of nephritic and diabetic origin treated by the oral administration of calcium lactate or calcium chlorid or both in doses of 12 to 18 gm. per day. Marked diuresis occurred as a result of this therapy in 6 cases; in the seventh diuresis occurred but was not attributed to the calcium therapy. They also found that large doses of calcium chlorid do not increase the amount of serum calcium. In several cases the chlorid was more effective than the lactate salt and they conclude that the former is the better diuretic. Keith *et al.* also report a significant diuresis in 1 case of subacute glomerular nephritis and in 1 of nephrosis.

This brief review of the literature indicates that calcium salts may cause diuresis in normal individuals as well as in individuals with a variety of diseases, including nephritis, cardiac failure, diabetes with edema, inflammatory effusions in the pleural sacs, hepatic cirrhosis with ascites and others. The influence of the calcium salts given orally in therapeutic doses seems to be related to the metabolism of water and inorganic salts in the tissues rather than directly to its effect upon the circulatory mechanism.

Our interest in studying the value of calcium chlorid as a diuretic was aroused by the striking results obtained in a case of heart disease with congestive failure and edema (Case III) when, after digitalis, diuretin and calomel began to fail or to be sluggish in their diuretic effect, calcium chlorid was most effective.

The chief object of our investigation has been to test the value of calcium chlorid as a diuretic and to determine its effect upon the circulatory mechanism as measured by clinical methods, particularly with reference to a possible digitalis-like action.

Present Investigation. Method. Crystalline calcium chlorid was administered in the form of a solution almost invariably, in 2.5 gm. doses diluted in 50 to 100 cc. of water. In experiments upon a normal individual doses of 5 gm. and 8 gm. each were taken. In the majority of cases the daily amount consisted of 15 gm. given in 6 doses of 2.5 gm. each at two-hour intervals. With the smaller doses the only handicap was the unpleasant taste of the drug; this may be avoided by giving the dry salt in capsules, each containing 0.5 gm. The larger doses of 5 and 8 gm. each caused a burning sensation in the epigastrium which was readily relieved by taking some food, less readily by drinking water. Diarrhea did not occur in any case; rather was there a tendency to constipation.

The "fluid intake" includes only liquids, like soups, milk, water, and not the water in solid or semisolid foods. In all but 2 cases

(II and XVII) the diet was a mixed ordinary hospital diet and salt was not restricted. In the few cases in which salt intake was restricted this fact is mentioned.

The pulse rate represents the resting pulse rate taken in the morning before breakfast at about seven o'clock.

The blood pressure was recorded by the auscultatory method and in cases of auricular fibrillation the point at which beats of an average rate of 80 to 90 per minute were first heard was recorded as the systolic pressure and that point at which beats at a similar rate ceased to be heard or became very faint was recorded as the diastolic blood pressure.

Vital capacity was determined with an ordinary water spirometer and is expressed in the tables in the terms of cubic centimeters of air, thus furnishing evidence of changes in the individual case.

By the term "digitalization" is meant the administration of 0.1 gm. digitalis leaf per 10 pounds of body weight within forty-eight hours and the usual maintenance dose prescribed in our clinic is 0.1 gm. of digitalis per day. Almost invariably digitalis leaf in pills of 0.1 gm. each is the preparation used; in a few instances digifolin was administered by mouth or intramuscularly.

Diuresis in Normal Persons During Calcium Chlorid Administration. CASE I.—H. N. S., male, aged twenty-six years. In order to determine the effect of calcium chlorid when administered to normal individuals with no cardiac or renal disease, two volunteers took the drug. The first series of observations on Case I were made under the following conditions: low calcium and salt-poor diet, which contained 0.093 to 0.140 gm. calcium and 1 to 2 gm. sodium chlorid per day, with a calorific value of 10 per cent or more over the basal requirements; continuation of subject's usual activities throughout the fifteen days of the experiment; blood pressure and vital capacity determined at midday before luncheon. The relatively low daily fluid intake of the subject during this experiment is his normal fluid intake. The calcium chlorid was taken in doses of 5 gm. diluted in 100 cc. of water three times a day with each meal for two days, on the third day 15 gm. in 200 cc. of water in one dose with the midday meal and during the next three days 8 gm. in 125 cc. of water three times a day, with each meal. Thus a total of 117 gm. was taken in six days.

The subjective symptoms were chiefly related to the unpleasant taste of the solution of calcium chlorid and the sensation of burning referred to the epigastrium which followed the larger doses. This discomfort lasted for one-half to one hour. With the smaller doses of 5 gm., each taken with a meal after about half of the food had been consumed, there was no epigastric burning. Occasional griping occurred during the days when the larger doses were being taken and there was a tendency to constipation; at no time did diarrhea occur.

The data in Table I show evidence of some diuresis during the course of calcium chlorid ingestion. The daily changes in the electrocardiogram are not conclusive evidence of the effect of calcium chlorid administered by mouth since similar changes occurred before and after this therapy.

TABLE I.—EFFECT OF CALCIUM CHLORID INGESTION IN A NORMAL PERSON. (CASE I.)

Date. 1923.	Calcium chlorid, gm.	Fluid intake, cc.	Urine, cc.	Body weight, kilos.	Blood pressure.		Vital capacity, cc air.	Heart rhythm.	Electrocardiogram.		*T* wave in Lead II, mv.
					Sys.	Dia.			Rate.	*P-R* interval second.	
Nov. 20	0	780	720	70.0	109	64	3600	Normal	80	0.16	+0.65
21	0	790	720	70.0	115	68	3600	Normal	70	0.16	+0.65
22*	0	790	700	70.0	110	65	3620	Normal	75	0.16	+0.70
23	15	790	820	70.0	120	70	3640	Normal	90	0.15	+0.50
24	15	780	1240	70.0	112	64	3700	Normal	70	0.17	+0.80
25	15	720	960	69.5	115	65	3690	Normal	80	0.16	+0.75
26	24	900	720	69.5	115	68	3800	Normal	75	0.17	+0.70
27	24	1420	2400	69.0	115	70	3790	Normal	70	0.17	+0.65
28†	24	960	1560	68.5	108	62	3800	Normal	75	0.17	+0.75
29	0	1200	1500	68.5	110	65	3810	Normal	90	0.16	+0.45
30	0	960	1250	69.0	112	65	3800	Normal	75	0.16	+0.45
Dec. 1	0	1000	950	69.0	115	71	3800	Normal			
2	0	920	800	70.0	115	61	3800	Normal			
3	0	960	720	70.5	110	60	3810	Normal			

* 8.5 mg. calcium per 100 cc. blood.
† 8 mg. calcium per 100 cc. blood.

TABLE II.—EFFECT OF CALCIUM CHLORID INGESTION IN A NORMAL PERSON. (CASE I.)

Date. 1924.	Fluid intake, cc.	Urine, cc.	Calcium chlorid, gm.	Date. 1924.	Fluid intake, cc.	Urine, cc.	Calcium chlorid, gm.
Mar. 18	2160	900	0	April 1	2100	1400	0
19	2100	950	0	2	1200	1400	0
20	2100	1150	0	3	1700	1100	0
21	1800	750	0	4	1600	900	0
22	1500	660	0	5	1800	850	0
23	2100	1200	0	6	1700	800	10
24	2000	1000	0	7	2100	650	10
25	2000	1400	0	8	2200	1350	10
26	1900	1300	0	9	2000	1300	10
27	1400	700	0	10	1900	1500	10
28	1400	600	0	11	2000	1400	10
29	1800	780	0	12	1900	1350	10
30	1800	900	0	13	2000	1400	10
31	1800	1500	0	14	1800	1200	10

There was apparently no significant change in vital capacity or blood pressure and none in the rate or rhythm of the heart; no extrasystoles were noted.

In Table II are represented the results in the same subject on a liberal mixed diet, a forced intake of 2 liters of water per day, and only 10 gm. of calcium chlorid per day. Only a tendency to diuresis is evident.

Acidosis was quite pronounced in this subject during the administration of the calcium chlorid, as proved by laboratory tests.

CASE II.—A. E. K., male, aged twenty-seven years, the second volunteer, also had a liberal diet and took about 2 liters of fluid per day, which is the amount he usually consumes. It is interesting to note that he eliminated about four-fifths of his fluid intake per day, under normal conditions. Calcium chlorid was administered in solution, 5 gm. in 100 cc. of water per dose, and 2 such doses were taken per day, one at the midday meal and the other at the evening meal. On the second day of this therapy a marked diuresis occurred. This however continued only for another day, then ceased and did not recur during the remaining seven days of calcium chlorid therapy (see Table III).

TABLE III.—EFFECT OF CALCIUM CHLORID INGESTION IN A NORMAL PERSON. (CASE II.)

Date. 1924.	Calcium chlorid, gm.	Fluid intake, cc.	Urine, cc.	Date. 1924.	Calcium chlorid, gm.	Fluid intake, cc.	Urine, cc.
Mar. 18	0	2100	2100	April 3	0		
19	0	2100	2150	4	0	2000	1875
20	0	2100	1900	5	0	2000	1800
21	0	2100	1900	6	0	2100	1900
22	0	2100	1900	7	10	2100	1875
23	0	2100	1925	8	10	2100	3200
24	0	2100	1625	9	10	2100	3000
25	0	1900	1700	10	10	2100	1800
26	0	1200	1400	11	10	2100	2000
27	0	2100	2100	12	10	2100	1820
28	0			13	10	2000	1490
29	0	2100	1800	14	10	2100	1900
30	0	2100	1800	15	10	2100	1900
31	0			16	10	2100	1750
April 1	0	1800	1450	17	10	2100	1800
2	0	2100	1900				

Discussion. In these two normal individuals the diuresis was slight or moderate in degree and its duration varied. Thus in Table I the diuresis is seen to begin on the second day of calcium chlorid therapy and to continue for two days after discontinuation of the drug. In Table II, however, it is seen that only slight if any diuresis occurred in the same subject with the administration of 10 gm. of calcium chlorid per day. The other normal subject, A. E. K., had a striking diuresis on the second day of calcium chlorid therapy but this ceased quite suddenly and in spite of continued ingestion of the drug there was no further diuresis.

Effect of Calcium Chlorid in Cases of Cardiac Failure. CASE III.—N. C. M., male, aged fifty-three years, a merchant, always very active, began to notice dyspnea on exertion in 1921. In February, 1922, his doctor found him to have a systolic blood pressure of 170. Cardiac failure with edema of the legs, ascites and congestion of the lungs first occurred in May, 1922, when he was found to have hypertensive heart disease with a blood pressure of 260 systolic and 160 diastolic. He subsequently had frequent recurrences of congestive failure. There was no evidence of chronic nephritis. He was digitalized in May, 1922, and continued to take an average of 0.2 gm. of digifolin per day. In addition to rest in bed and digitalis, diuretics were always necessary in the treatment of the attacks of congestive failure with general anasarca. He responded very readily to calomel, 0.7 to 1 gm. per day for three days; sometimes diuretin or theocin was given following a course of calomel. These diuretics produced very marked diuresis, as much as 6½ liters of urine a day being passed until all the edema, ascites and hydrothorax disappeared.

In April, 1923, he became less responsive to these diuretics and continued to gain weight, with increasing edema even while taking calomel. A diuresis followed the second of two courses of calomel. Edema did not completely disappear and diuresis having ceased after the second of these two courses of calomel it was decided to try calcium chlorid; this was the first case in which we used this drug as a diuretic.

Well-marked diuresis occurred promptly after the beginning of and during the administration of calcium chlorid by mouth and stopped when this was discontinued only to begin again with resumption of the calcium chlorid therapy. Moreover, a constant negative fluid intake and output balance was maintained by the regular administration of calcium chlorid by mouth, 10 to 15 gm. every other day alternating with 0.2 gm. of digitalis. This régime was continued for two weeks after he left the hospital, then he took digitalis 0.2 gm. every day and calcium chlorid 12 gm. only once a week. He remained free from edema for about six weeks and then in spite of daily doses of digitalis (0.2 gm.) and calcium chlorid (12 gm.) he again developed general anasarca and died on July 23, 1923.

This patient derived much benefit from diuretics. When calomel, theocin and diuretin began to fail in their effectiveness, calcium chlorid produced very prompt diuresis. These results led us to try the use of calcium chlorid as a diuretic in other cases of cardiac failure with edema as well as in 1 case of polyserositis and in 1 case of ascites due to cirrhosis of the liver, conditions in which a number of investigators have reported calcium chlorid to be an effective diuretic.

CASE IV.—J. B. (Hospital No. 260088), male, aged fifty-one years, a coal miner, noticed the gradual onset of shortness of breath on exertion in 1921. After "a cold" in February, 1922, he had swelling of the legs; general weakness and shortness of breath became more marked. After a rest of two weeks he felt better, but not well enough to return to coal mining. He changed his occupation to shoe repairing. In September, 1923, dyspnea and general weakness were very marked; edema of the extremities and "filling up" of the abdomen recurred. After three weeks of rest and treatment with "medicines" he felt well enough to be up and about. In November, 1923, he again became "sick" with swelling of the legs and abdomen; during two weeks of treatment at home with rest in bed and "medicines" he grew steadily worse so that he was brought to the hospital in a desperate condition. He appeared to be in a moribund state, with very intense cyanosis, marked general anasarca, ascites and hydrothorax. There was no evident enlargement of the heart, the blood pressure was 120 systolic and 90 diastolic, the heart sounds were of fair quality, and there was no evidence of valvular or pericardial pathology; there were frequent extrasystoles with pulsus bigeminus for long periods of time (hours). He had marked emphysema and this condition together with possible anthracosis were considered as important factors in the causation of the deep cyanosis.

Soon after his arrival in the ward abdominal paracentesis was performed and a liter of pale straw-colored fluid was removed; 0.8 gm. of digifolin were administered intramuscularly during the first twenty-four hours and because he had nausea only 0.2 gm. of digitalis leaf per day was given during the next three days. This had no noticeable beneficial effect: on several occasions he lapsed into unconsciousness with very weak pulse and intensified cyanosis; the prompt administration of oxygen by the simple funnel method seemed to revive him.

On the eighth day after his admission to the hospital calcium chlorid therapy was started. From the data in Table II it appears that marked diuresis occurred during this therapy and the hydrothorax disappeared; the patient's general condition improved with dramatic rapidity. At the end of three weeks' stay in the hospital he was able to be up and about the ward. There was no perceptible diminution in cyanosis, the blood pressure remained at a relatively normal level, two attacks of paroxysmal fibrillation occurred and ventricular extrasystoles persisted, but were less frequent. There was no change in the size of the heart as measured by percussion, and the heart sounds did not become altered. He became much less orthopneic and the vital capacity increased by more than 300 per cent; whereas the pulse was relatively rapid before marked diuresis began, it became slow and less fluctuating in rate during and after the diuresis. It is doubtful whether this was the result of the action

of calcium chlorid on the heart directly. During the administration of this drug for five days prior to the onset of marked diuresis the pulse remained as it was before calcium chlorid therapy was begun. The diminished frequency of ventricular extrasystoles also began only after the onset of diuresis and it is presumed as most likely that in this case the reduction in number of extrasystoles may have been due to either the excretion of all digitalis which the patient had taken before and after his entrance into the hospital, or, if digitalis was not the cause of the extrasystoles, to improvement in circulation by reduction of edema *per se*.

The evidence in this case may be summarized as follows: probable arteriosclerotic heart disease with cardiac failure and marked general anasarca; digitalis given in large doses (probably causing pulsus bigeminus and nausea) failed to cause diuresis or any clinical improvement in the patient's serious condition; five days after the beginning of calcium chlorid therapy a marked diuresis began; this persisted until all the edema, ascites and hydrothorax had disappeared and some diuresis continued for six days after the drug was discontinued; coincidentally with the diuresis the patient's clinical condition changed so that he was able to be up and about. It is presumed from the evidence in this case that if calcium chlorid were responsible for the improvement in this patient's condition its effect consisted in producing a diuresis not primarily by an effect upon the heart itself, but by influencing water metabolism. The improvement in circulation is, therefore, considered as secondary to the reduction of edema.

Case V.—C. W. C., (Hospital No. 260263), aged seventy-five years, male, janitor, was first observed in 1920 when he was found to have arteriosclerotic and hypertensive heart disease, auricular fibrillation and congestive failure with edema of both lower extremities and congestion of both lungs. He did not complain of dyspnea or orthopnea. Following digitalization and while continuing to take 0.1 gm. digitalis leaf per day he remained free from edema until January, 1923, when he was admitted to the hospital ward with general anasarca. This had been developing during the previous month when he ceased taking digitalis because the supply of pills became exhausted and he procrastinated in buying more of them. Fibrillation continued but the pulse rate was quite low, varying between 50 and 60 per minute, apparently due to an organic lesion causing *A-V* block. There was no evidence of chronic nephritis.

On the third day after admission a thoracoparacentesis was performed and 1200 cc. of transudate were removed. Two days later calcium chlorid therapy was begun. A prompt diuresis occurred soon after the beginning of and during calcium chlorid administration. There was no appreciable change in heart rhythm or rate, or in blood pressure, and vital capacity increased only

slightly; no change was detected in the electrocardiographic curves which could be ascribed to the effects of calcium chlorid on the heart directly, and it is therefore inferred that the diuresis was caused by the influence of calcium chlorid on water metabolism in the tissues.

CASE VI.—W. G., (Hospital No. 260230), male, aged sixty-five years, clerk. This patient stated that he was in very good health until four days before he came to the hospital (in December, 1923), when he began having a dry cough and discovered that his feet and ankles were swollen. He was found to have arteriosclerotic and hypertensive heart disease, auricular fibrillation and congestive failure with a moderate amount of edema of both legs and feet and some congestion at the bases of both lungs. He also had marked emphysema. There was no evidence of nephritis.

During the first nine days he was merely kept in bed on a liberal diet with restriction of the total fluid intake to 2 liters per day. During this period of time all edema and congestion disappeared but no very marked diuresis occurred. Then, during the administration of calcium chlorid, the fluid intake and output balance changed from positive to negative and continued so until the cessation of this therapy when a positive balance was reëstablished and persisted later during digitalization.

In this case calcium chlorid therapy caused diuresis in the absence of any evident edema, without effecting any change in the heart rate or rhythm, or any change in the shape of the electrocardiographic curve or in vital capacity. Furthermore the absence of diuresis during digitalization suggests that calcium chlorid has not a digitalis-like action but that its effect is on water metabolism in the tissues rather than on the circulatory mechanism directly.

CASE VII.—E. M., (Hospital No. 256940), female, aged twenty-four years, housewife, at the age of sixteen had rheumatic fever and two years later, shortly after she was married, became aware of shortness of breath on exertion. Two normal pregnancies and one miscarriage were unassociated with cardiac failure. In the fifth month of the most recent pregnancy she began to have marked dyspnea on going up one flight of stairs, edema of both legs and feet and cough with occasional bloody sputum. She was admitted to the hospital in June, 1923, two weeks after a normal delivery and was found to have rheumatic heart disease with mitral stenosis (marked) and aortic regurgitation (slight), congestive failure with ascites and edema. She also had phlebitis of the left brachial and internal jugular veins. There was no evidence of nephritis.

Digitalization and 4 gm. diuretin, the latter given in one day, had no significant diuretic effect. The administration of calcium chlorid one week later brought about a negative balance of fluid intake and output which continued for one day after the cessation

of this therapy; edema and ascites disappeared. In spite of continuation of digitalis to maintain a state of digitalization a positive balance of fluid intake and output became reëstablished. The pulse rate became somewhat slower only after twelve days of rest in bed and nine days after digitalization; there was no significant change in blood pressure.

From the evidence in this case it may be inferred that the effect of digitalis on the circulatory mechanism was not enough to cause diuresis, but that with the aid of the influence of calcium chlorid on water metabolism in the tissues the output of urine was greatly increased and edema and ascites disappeared.

CASE VIII.—R. B., (Hospital No. 253977), male, aged sixteen years. Since the age of seven he had been having recurrent attacks of rheumatic fever and some choreiform movements in the intervals between these attacks. He first came under our observation in January, 1923, with rheumatic fever and was found to have rheumatic heart disease with mitral stenosis and aortic regurgitation. In spite of tonsillectomy which was performed in February, 1923, he had another attack of rheumatic fever the following month while at home. In April, 1923, was again taken into the hospital with rheumatic pericarditis and congestive failure with edema of feet and legs, ascites and congestion at the bases of both lungs; at this time he also developed bronchopneumonia. With rest in bed, salicylates, digitalization and recovery from the respiratory infection, the edema, ascites and congestion of the lungs gradually disappeared and he was again sent home to convalesce, with instructions to continue taking 0.1 gm. digitalis per day in order to maintain digitalization. Contrary to advice, however, he discontinued the digitalis and returned to the out-patient clinic five weeks later with marked ascites, edema of the legs and congestion at the bases of both lungs. He was sent home with instructions for digitalization and constant rest in bed. He took the digitalis but a week later edema had increased and he was more orthopneic than ever before. Consequently he again entered the hospital and the results of digitalis and calcium chlorid therapy were similar to those in Case VII inasmuch as in the presence of normal rhythm digitalis caused little or no diuresis, while calcium chlorid was more effective.

In Table IV are represented the results of the intravenous injection of 75 cc. of a 2 per cent solution of calcium chlorid in this case (VIII); an increased production of urine must have started soon after the injection, for 350 cc. were eliminated within an hour and another 400 cc. in the following two hours. Electrocardiograms taken just before and immediately after the injection of calcium chlorid showed no differences. These results as regards diuresis are similar to those obtained by Dr. Koehler while working in the Massachusetts General Hospital. He has made numerous obser-

vations of this nature and has found that the calcium content of the blood remains slightly elevated only for one-half to one and a half hours after the injection of calcium chlorid and that there is a coincident moderate but definite decrease in the pH of the blood. These observations are in accord with those of other authors who have investigated these problems.

TABLE IV.—INTRAVENOUS INJECTION OF 75 CC. OF 2 PER CENT SOLUTION CALCIUM CHLORID AT THE RATE OF 5 CC. PER MINUTE.

Time, P.M.		Urine, cc.	Electrocardiogram, etc.
3.30	....	..	Normal rhythm; rate, 110; *T* wave in Lead II = −0.1 mv.; *P–R* = 0.26 seconds.
4.00	....	75	
4.35 to 4.50	Injection of calcium chlorid		
4.55	....	..	Electrocardiogram; exactly the same as at 3.30.
5.30	....	..	Desire to pass urine.
5.45	....	350	
6.30	....	310	
7.30	.....	90	

Discussion. In all of these 6 cases of cardiac failure with edema some combination of the usual measures of causing diuresis was tried before the administration of calcium chlorid was begun. Rest in bed alone or with digitalization, and sometimes the addition of calomel or diuretin, or both, were either moderately or little if at all effective in reducing the edema. With calcium chlorid therapy, diuresis began on the first to the fifth day and in 3 cases continued for one or more days after the drug was discontinued. No changes occurred in pulse rate, blood pressure or vital capacity which could be attributed to the effect of the calcium chlorid therapy on the circulatory mechanism directly; nor can we unreservedly attribute to it the slight changes in the electrocardiogram. It would appear therefore that calcium chlorid when taken by mouth is not similar to digitalis in its action but causes diuresis by influencing water metabolism in the tissues.

CASE IX.—L. M., (Hospital No. 261196), male, aged fifty-four years, tailor, was a moderately obese man who had had asthma for twenty years. He was first observed in the hospital in 1920, when it was found that in addition to asthma and emphysema he had arteriosclerotic heart disease, angina pectoris (rare attacks) and some congestive failure. His symptoms of dyspnea on exertion, orthopnea, general weakness and slight swelling of the ankles gradually increased in severity. The attacks of angina pectoris became more frequent, as many as four per week. In February, 1924, he was admitted to the hospital with congestive failure, edema of legs and feet and

congestion at the bases of both lungs. There was no evidence of nephritis. The cardiac rhythm was normal.

With rest in bed and an ordinary mixed diet he slowly improved and the edema decreased while the output of urine increased slightly. When calcium chlorid therapy was begun 6 days after admission to the ward some edema over the sacrum was still present, and with the marked diuresis which followed, this and the crackling rales at both lung bases also disappeared. Some diuresis continued for eight days during which the patient received no medication; with the resumption of calcium chlorid administration no diuresis occurred.

The data in this case indicate a diuretic influence of calcium chlorid, although diuresis occurred after the first course and not after the second. During neither period was there any significant change in heart rate or rhythm, in the electrocardiographic curve or in vital capacity which could be attributed to the direct action of calcium chlorid on the circulatory mechanism. If the diuresis during and after the first course of calcium chlorid therapy was due in part to the action of this drug it is fair to infer that the effect was on water metabolism in the tissues and not on heart action.

CASE X.—A. J. P., (Hospital No. 260490), male, aged fifty-two years, butcher, became aware of dyspnea on exertion subsequent to a cold with sore throat, cough and some fever in January, 1924. He continued at work lifting quarters of beef, weighing as much as 150 pounds, until he came into the hospital the following March, when he was found to have arteriosclerotic heart disease, auricular fibrillation and slight congestive failure evidenced by moist crackling rales at the bases of both lungs. There was no ascites or edema of the extremities and no evidence of nephritis.

A moderate diuresis occurred for 2 days with a régime of complete rest in bed only and continued without any significant increase during 10 days of calcium chlorid administration (15 grains daily). The diuresis ceased on the second day after discontinuing calcium chlorid and subsequent digitalization with effective slowing of the heart rate had no diuretic effect.

The heart rate became somewhat slower during rest and calcium chlorid therapy, but a relatively large apex-radial pulse deficit continued until after digitalization. Electrocardiographic tracings showed certain slight but definite changes; the *T* wave in Lead II was isoelectric before and somewhat negative during and after calcium chlorid therapy and the rate of auricular fibrillation became somewhat slower.

There was no significant change in blood pressure and after the patient had become proficient in the practice of forced expiration no appreciable change in the vital capacity occurred.

Restoration to normal rhythm with quinidin sulphate therapy

was not accompanied by any objective signs of improvement in cardiac function, but the patient felt greatly improved. He was no longer conscious of his heart beating and felt "as if everything were normal again."

The evidence in this case indicates that calcium chlorid had little or no influence on the heart muscle, the slowing of the ventricular rate and the slight negativity of the *T* wave in Lead II probably resulting from other causes. The constant rest in bed alone seems to have been responsible for the moderate diuresis although it is possible that calcium chlorid had some additional diuretic influence.

CASE XI.—M. C. F., (Hospital No. 259937), female, aged sixty-three years, cashier, during the summer of 1923 began to notice palpitation on exertion and also had to begin using two pillows instead of one to avoid slight difficulty in breathing at night. Otherwise she felt well and was able to carry on her work as a cashier. Six weeks before coming to the hospital she had a slight cold with several chills and about this time began to notice swelling of feet and legs which extended up to thighs and abdomen in a few weeks. When she entered the hospital in December, 1923, she was found to have arteriosclerotic and hypertensive heart disease and congestive failure with general anasarca. There was no evidence of nephritis. As a result of rest in bed, an ordinary mixed diet, and slight limitation of total fluid intake she had a moderate diuresis, lost much weight, and the edema and ascites entirely disappeared in eleven days. Subsequently, administration of calcium chlorid for three days did not cause any significant diuresis.

This case again illustrates the effect of rest alone in improving cardiac function with consequent reduction of edema. No striking objective signs of improvement in cardiac function were observed, the pulse rate remained between 75 and 85 per minute, but there was some increase in vital capacity and an increase in pulse pressure as a result of increase in the systolic and decrease in the diastolic pressures.

There was slight diuresis on the third, the last, day of calcium chlorid therapy, but none occurred during the previous two days or after the drug was discontinued.

CASE XII.—E. H., (Hospital No. 261936), male, aged thirty-nine years, farmer, at the age of twenty-nine years had an attack of rheumatic fever which caused him to remain in bed for seven months; subsequently he had several milder attacks. At the age of thirty-five he began to notice palpitation and dyspnea on exertion and had to cease working. During the next four years these symptoms became progressively more marked. In January, 1924, two months before he came to the hospital, he took to bed because of marked dyspnea and orthopnea, swelling of legs and abdomen, and cough with bloody sputum.

He was found to have rheumatic heart disease, mitral stenosis and regurgitation, cardiac enlargement and signs suggesting adhesive pericarditis. There were right hydrothorax, congestion in base of left lung, ascites, and edema over the sacrum and of both lower extremities below the hips. The patient appeared very sick; he was cyanotic and markedly orthopneic.

Marked diuresis and subjective improvement developed gradually during a week of complete rest in bed, limitation of fluids, Karrel diet and digitalization. As the anasarca diminished the extent of diuresis waned until a positive fluid intake and output balance became established.

All therapeutic measures were then discontinued for three days and thereafter calcium chlorid was administered for five days; a slight diuresis occurred only on the second and third days of this therapy. When administration of calcium chlorid was started the patient was feeling quite comfortable and there was no apparent hydrothorax, ascites or edema of the extremities; crackling rales at both lung bases persisted however.

There were no apparent changes in the circulatory mechanism and the subjective symptoms were not noticeably changed by the calcium chloride therapy.

Case XIII.—C. P., (Hospital No. 259245), male, aged fifty-seven years, laborer, since his illness with typhoid fever in 1917 had had shortness of breath on exertion and edema of the feet and legs which increased during the day and diminished over night. In September, 1923, he came to the out-patient cardiac clinic and was found to have arteriosclerotic heart disease with congestive failure (edema over both shins); the electrocardiogram showed sinoauricular bradycardia, the rate varying from 45 to 55 per minute. He was digitalized and continued to take a maintenance dose of 0.1 gm. and 0.2 gm. of digitalis leaf on alternate days. His symptoms and edema were somewhat diminished in severity but he returned in two weeks with persistent edema of both legs. Diuretin, 3 gm. per day for a week, was added to the digitalis therapy and this resulted in the entire disappearance of edema and the loss of 3.5 kilos of weight in one week. However he returned again the next week with a re-accumulation of edema of both legs and was taken into the hospital.

In this case calcium chlorid given together with digitalis at that time for 5 days was associated with but slight diuresis. There were no significant changes in rhythm or in vital capacity. In the electrocardiogram the *P-R* interval became lengthened, while the negative *T* wave in Lead II tended to become positive.

Case XIV.—H. P., (Hospital No. 260405), male, aged twenty-one years, was first observed in May, 1920, when he was found to have

rheumatic heart disease, mitral stenosis and regurgitation, aortic regurgitation, and fibrinous pericarditis. During the next three years he continued a well-ordered convalescent existence, being greatly limited in his activity by marked shortness of breath on exertion. On several occasions after undue exertion he became very weak, with feet and legs swollen, and had to remain in bed. For the first four or five days of rest in bed he would continue to feel weak and orthopneic, passed very small amounts of urine and the swelling would increase; then on the fifth or sixth day he would suddenly begin to pass a great deal of urine, sometimes with frequency (every fifteen minutes). He took little digitalis (never more than 30 drops of tincture per day) during these periods.

In January, 1924, he came to the hospital again in a state of marked cardiac failure with general anasarca and orthopnea. In addition to the previous cardiac findings he also had auricular fibrillation. There was no evidence of nephritis.

During eight days of calcium chlorid therapy, and restricted low fluid intake, the amount of urine per day was about equal to the total fluid intake excepting on the eighth day, when more marked diuresis occurred. The slight diuresis during the first seven days can hardly be ascribed to the calcium chlorid therapy alone and it is more likely that the rest in bed and restricted low fluid intake were chiefly responsible. The patient did not improve symptomatically and edema seemed to increase. The heart rate became somewhat slower (probably from complete rest in bed), but it remained relatively rapid and the large apex-radial pulse deficit persisted. The change in the *T* wave of Lead II from slightly diphasic to upright may be ascribed to elimination of the digitalis which he had taken before coming to the hospital. Because of the poor condition of the patient it was necessary to apply more orthodox measures for his relief and after digitalization and the administration of large doses of diuretin, a marked diuresis occurred, the apex-radial pulse deficit disappeared, edema gradually became reduced, he lost 10 kilograms in weight and there was a marked subjective improvement in symptoms.

The evidence in this case indicates that calcium chlorid has not a digitalis-like action in the treatment of auricular fibrillation with cardiac failure and edema.

CASE XV.—S. S., (Hospital No. 263703), female, aged sixty-two years, housewife, an obese, short, elderly woman, complained of dyspnea and palpitation on exertion, and nocturia (3 or 4 times), which she began to notice in February, 1924. Four months later she came to the hospital and was found to have hypertensive and arteriosclerotic heart disease with slight congestive failure (edema of feet and ascites) and general arteriosclerosis. Heart rhythm was normal. Renal functional tests (Schlayer concentration test,

chlorid excretion, and nonprotein nitrogen in the blood) did not suggest nephritis but were compatible with passive congestion and arteriosclerosis of the kidneys.

Calcium chlorid together with the maintenance dose of digitalis was given for five days; no diuresis occurred until the fifth day and then it ceased with the discontinuation of calcium chlorid therapy. While this slight temporary diuresis may have been caused by the calcium chlorid therapy we can draw no definite conclusions from the data in this case.

CASE XVI.—H. H., (Hospital No. 263735), male, aged fifty-nine years, janitor, an elderly obese man, had been suffering from dyspnea on exertion for about five years. His symptoms became greatly aggravated following pneumonia a year and a half before coming under our observation in June, 1924. For the last year he had been confined to bed because of marked swelling of the legs and abdomen, and orthopnea. Fluid had been oozing through the skin of his legs and this was followed by a very painful dermatitis. He also gave a history of typical attacks of angina pectoris. He was found to have hypertensive and arteriosclerotic heart disease, and marked congestive failure with general anasarca. Tests of kidney function were consistent with marked passive congestion of the kidneys, there being no data pointing to acute or chronic nephritis.

Neither diuretin, digitalis nor calcium chlorid had any significant diuretic effect on this patient. Neither digitalis nor calcium chlorid had any effect on blood pressure or on pulse rate. Edema increased and he grew steadily weaker and died of cardiac failure on the twentieth day of his stay in the hospital. The significant finding at autopsy was a large heart; the kidneys presented a typical appearance of chronic passive congestion without any evidence of acute or chronic nephritis.

CASE XVII.—R. J. B., (Hospital No. 259681), male, aged forty years, seaman, had had "attacks of kidney trouble" during the past eight years, corresponding to acute and subacute nephritis; he was treated with salt-free, low-protein diet and rest in bed for periods varying from days to weeks. Dyspnea on exertion and nocturnal paroxysms of orthopnea had occurred only in the last two years. He had been in bed for six weeks before coming to the hospital, presenting evidence of hypertensive heart disease with congestive failure, chronic nephritis (nitrogen retention type) and a moderate degree of uremia. He was markedly orthopneic, both lower extremities and the sacral region were edematous, and moist crackling rales were heard at the bases of both lungs. True pulsus alternans was detected by the blood-pressure method; halving of the pulse rate occurred between 260 and 240 mm. of mercury, systolic pressure.

Treatment with salt-free, low-protein diet, diuretics, including calcium chlorid, and digitalis had no beneficial effect. In the fifth week of his stay in the hospital he developed erysipelas, uremia became more marked and he died two weeks after the onset of this infection. Permission for an autopsy was not granted.

In this case of edema resulting from cardiac failure and chronic nephritis, neither calcium chlorid together with a salt-free, low-protein diet nor digitalis caused diuresis; nor had these measures any discernible effect on the circulatory mechanism directly. The changes which occurred in the electrocardiographic curve during calcium chlorid administration are similiar to those which were observed immediately before and after this therapy and therefore cannot be ascribed to it but were due more probably to the retention of toxic substances which caused the uremia. (See paper by Wood and White.)

Discussion. The above 9 cases include 5 in which diuresis occurred during calcium chlorid therapy. In 2 of these (1 with normal rhythm and the other with auricular fibrillation) it occurred in association with the beginning of the régime of rest in bed, and therefore the diuresis cannot be entirely attributed to the calcium chlorid although this drug may have had some influence. In the other 3 a slight transient diuresis occurred after all apparent edema had been reduced with other measures, namely rest alone in 1 case and with the addition of digitalis in the other 2. Of the remaining 4 cases, 1 with rheumatic heart disease, auricular fibrillation and anasarca failed to respond to calcium chlorid but digitalization and the administration of diuretin was followed by marked diuresis and by great improvement in the patient's condition. Two cases of cardiac failure without nephritis and 1 with nephritis and uremia did not respond to any medication, digitalis, diuretin, calcium chlorid, alone or in combination.

In none of these 9 cases was there any clinical evidence to indicate that calcium chlorid administered by mouth had any effect on the circulatory mechanism. The slowing of the heart rate in the 2 cases of auricular fibrillation may be accounted for by the rest in bed alone. The persistence of a large apex-radial pulse deficit in both of these cases and the fact that no diuresis or other beneficial effect occurred in the one with anasarca while digitalization and the administration of diuretin were followed by marked diuresis and general improvement indicate that calcium chlorid had not a digitalis-like action in cases with auricular fibrillation.

Effect of Calcium Chlorid in a Case of Tubercular Polyserositis. CASE XVIII.—H. A. S., (Hospital No. 260418), female, aged fifty-five years, housewife, had polyserositis, pulmonary tuberculosis, cardiac enlargement and auricular flutter. Her illness began grad-

TABLE V.—EFFECT OF CALCIUM CHLORID AND OF DIGITALIS IN A CASE OF TUBERCULOUS POLYSEROSITIS AND AURICULAR FLUTTER WITH VARYING DEGREES OF BLOCK. (CASE XVIII).

Date, 1924.	Therapy.	Fluid intake, cc.	Urine, cc.	Body weight, kilos.	Pulse rate.	Blood pressure.		Vital capacity, cc. air.	Paracentesis. Electrocardiograms.
						Sys.	Dia.		
Jan. 4	.....	...	...	...	..	..	..	....	Abdominal paracentesis, 5 liters. Auricular flutter; auricular rate, 260; 2:1 to 4:1 block; ventricular rate, 80 to 125; *T* wave in Lead II diphasic.
5	Calcium chlorid, 15.0 gm.	1400	600	37.3	108	..	..	600	
6	Calcium chlorid, 12.5 gm.	1900	900	...	100	..	..	....	Right thoracoparacentesis, 900 cc.
7	Calcium chlorid, 12.5 gm.	2400	700	...	100	120	85		
8	Calcium chlorid, 12.5 gm.	2100	600	41.3	90	..	..	600	
9	Calcium chlorid, 12.5 gm.	1800	300	41.5	80	..	..	....	Electrocardiogram same as on January 4, except ventricular rate, 100 to 125.
10	Calcium chlorid, 12.5 gm.	2000	500	41.5	120	..	..	650	
11	Calcium chlorid, 12.5 gm.	1800	400	...	110	110	80		
12	Calcium chlorid, 12.5 gm.	1600	500	...	120	..	..	750	
13	Calcium chlorid, 12.5 gm.	2100	600	...	110				
14	Calcium chlorid, 12.5 gm.	2100	600	...	110				
15	Calcium chlorid, 12.5 gm.	1800	750	...	120				
16	Calcium chlorid, 12.5 gm.	1300	650	...	100				
17	Digitalis, 0.6 gm.	2600	900	44.0	108	115	85	700	
18	Digitalis, 0.1 gm.	2500	1000	...	122	..	..	....	Electrocardiogram same as on January 4.
19	Digitalis, 0.1 gm.	2250	800	...	118	..	..	750	Electrocardiogram same as on January 18.
20	Digitalis, 0.1 gm.	1700	700	45.3	100	..			
21	Digiatlis, 0.1 gm.	1200	600	...	90	120	80		
22	No medication	1500	700	...	100	..	..	....	Auricular fibrillation (coarse); ventricular rate, 90; inverted *T* wave in Lead II = − 0.2 mv.
23	No medication	1500	600	...	90	..	..	700	Abdominal paracentesis, 5 liters.
24	No medication	1500	650	...	110	115	80		

ually six years before entrance to the hospital on January 4, 1924; fluid accumulation in abdomen and chest had been progressive, requiring paracentesis several times. There was slight fever only. Hemoptysis had occurred two years previously.

On physical examination at the time of entrance to the hospital ward she was emaciated and showed signs of old tubercular processes at both apices, marked ascites, bilateral pleural effusion, enlargement of liver and of heart, and auricular flutter with auricular rate of 270 and ventricular rate varying from 80 to 130. Abdominal and thoracic paracentesis yielded much fluid (5000 cc. from former and 900 cc. from latter) with specific gravity of 1011 to 1015 and lymphocytic smear.

Calcium chlorid therapy was begun January 6, and continued for eleven days at a dose of 15 gm. the first day, 10 gm. the next four days and 7½ gm. thereafter. It was absolutely without effect either on the ascites, pleural effusion, weight of patient, auricular flutter or electrocardiogram. (See Table V.) Fluid accumulated steadily in the serous cavities in spite of its use. On January 18 the calcium chlorid was discontinued and digitalis was begun and continued for three days. A reduction of the ventricular rate resulted without appreciable improvement in the patient's condition. Ascites reaccumulated.

This case of polyserositis showed no beneficial effect from calcium chlorid.

Effect of Calcium Chlorid in a Case of Hepatic Cirrhosis with Ascites. CASE XIX.—F. H. S., (Hospital No. 261984), male, aged forty years, automobile mechanic, had alcoholic cirrhosis of the liver with marked ascites and jaundice. He died on the tenth day of his stay in the hospital following a severe hemorrhage from an esophageal varicose vein.

There was no diuretic effect from calcium chlorid. It is interesting that although there was no evidence suggestive of nephritis of either the chlorid or nitrogen-retention type, the urine output remained about the same during large or small fluid intake. Fluid reaccumulated after both abdominal paracenteses.

In this case of hepatic cirrhosis with ascites calcium chlorid affected neither the amount of ascites already present, the reaccumulation of ascitic fluid nor the elimination of urine.

Discussion. These 2 cases belong to the types in which Blum and his associates, and subsequently other authors, have observed beneficial results from calcium chlorid therapy. The administration of calcium chlorid had no apparent effect on the case of probable tuberculous effusion into serous cavities, nor on the patient with hepatic cirrhosis and marked ascites. In these cases also there was no evidence of any influence of calcium chlorid on the circulatory

mechanism; the auricular flutter in Case XVIII was not affected in any way.

TABLE VI.—CHANGES IN HEART RATE, RHYTHM AND ELECTROCARDIOGRAM DURING CALCIUM CHLORID THERAPY.

	Change.	Cases in which change occurred.
Rhythm	Normal to abnormal	None.
	Abnormal to normal	None.
Rate	Increase	None.
	Decrease	IV, X, XIV.
Extrasystoles	Newly produced or increased	None.
	Decrease	IV.
P wave	Positive	IV.
	Negative	None.
P–R interval	Lengthened	XIII, IV.
	Shortened	XIII, IV.
Q–R–S complex, Lead II	Slurred or notched	IV.
	Widened	None.
T wave, Lead II	Positive	I, IV, VI, XIII, XVII.
	Negative	I, V, VI, XIV, XVII.

Effect of Calcium Chlorid Administration on the Electrocardiogram. In 11 cases electrocardiograms were taken before, during and after calcium chlorid therapy and some change or other was noted in 8. In no case did any change in rhythm occur and the variations that were observed were not uniform. In 3 cases there was a decrease in rate which, however, is to be attributed to the fact that this change occurred during the first part of the patient's stay in the hospital under a régime of constant rest in bed. In Case III a prolongation, then shortening, of the *P-R* interval and also an increase in positivity of the *T* wave in Lead II occurred during calcium chlorid therapy. In Cases I, VI, and XVII the *T* waves of Lead II varied in their changes from day to day, sometimes toward negativity and at other times toward positivity. Case XVII had uremia, and, as Wood and White have shown, such changes in the *T* wave occur in cases of nitrogen retention probably as a result of toxic effects on the myocardium. The electrocardiogram of Case XIV showed auricular fibrillation without any change in this rhythm but slight negativity of the *T* wave in Lead II. Case IV showed numerous changes, including prolongation of the *P-R* interval, increased positivity and notching of the *P* wave, increased negativity of the *T* wave and change from slurring to notching of the *R* wave in Lead II; in this case the frequency of extrasystoles and the heart rate were diminished only after marked diuresis had caused much improvement in the general condition of the patient. In view of the fact that in the other 18 cases the heart rate was not affected by calcium chlorid therapy, it is inferred that in this case the slowing of the heart rate was secondary to the effect of diuresis on the circulatory mechanism rather than that the

slowed heart rate was responsible for the diuresis. As regards the other changes it is probable that they were as likely due to sclerotic changes in heart muscle as to the direct effect of calcium chlorid upon the myocardium.

In view of the lack of uniformity of the changes and the simultaneous existence of other variable factors it is not possible to draw any absolute conclusions as to the effect of oral administration of calcium chlorid upon the electrocardiogram. It appears probable that there are no direct effects.

In Case IX electrocardiograms taken just before and immediately after the intravenous injection of 1.5 gm. of calcium chlorid showed no change as a result of this procedure.

Summary. The administration of large doses of calcium chlorid by mouth in two normal individuals was accompanied by a moderate temporary diuresis and no apparent significant changes in the circulatory mechanism as studied by clinical methods. Acidosis accompanied the diuresis.

Of the cases of heart disease with congestive failure and edema a group of 6 which had not responded well to treatment with rest in bed only, or together with digitalis and various diuretics, showed a well-marked diuresis during the administration of calcium chlorid. The diuresis began on the first to the fifth day of calcium chlorid therapy and in 3 cases did not cease until this drug had been discontinued for one or more days. In another group of 9 similar cases (excepting 1, XVII, who also had chronic nephritis and uremia) no significant diuresis occurred which could be attributed to calcium chlorid and in 3 of these digitalis alone or together with calcium chlorid or other diuretics also failed to cause diuresis. One case of this group (XIV), a patient with auricular fibrillation, after eight days of calcium chlorid therapy without beneficial effect responded readily and well to digitalization and the administration of diuretin.

In 2 miscellaneous cases, namely, 1 with probable tuberculous polyserositis and another of hepatic cirrhosis with marked ascites there was no diminution of the amount of fluid in the serous cavities nor was the continued accumulation of the fluid arrested by calcium chlorid therapy.

Data obtained upon heart rate, blood pressure, and vital capacity showed no evidence of direct effect of calcium chlorid administration upon the circulatory mechanism. Whereas some changes or other were noted in the electrocardiograms of 8 patients, there was no effect on rhythm or rate and the variations were not consistent either in different cases or in individual cases. Other variable factors, like recovery following previous digitalis therapy, uremia, improvement in circulation with marked diuresis from constant rest in bed, etc., were present in these cases and therefore it is not possible to draw any definite conclusions as to the effect of calcium chlorid

therapy on the electrocardiogram. It is obvious however, that calcium chlorid has no digitalis-like action upon the heart. From this it may be inferred that the diuretic effect of calcium chlorid is due to its influence upon water metabolism in the tissues rather than upon the circulatory mechanism.

In no case did we observe any deleterious effects on the patient's condition as a result of calcium chlorid therapy.

Conclusions. 1. In cases of cardiac failure with edema in which constant rest in bed, digitalization, and the administration of various diuretics have not resulted in a satisfactory diuresis, calcium chlorid may be employed as a diuretic.

2. No deleterious effects were observed from the oral administration of calcium chlorid, 10 to 15 gm. per day, in any of the cases studied.

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THE VALUE OF VENESECTION IN THE TREATMENT OF THE DECOMPENSATED HEART.

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In reviewing the early history of medicine, there is a striking periodicity of certain forms of treatment in disease. Some methods have been entirely empirical and their value and usage has depended largely upon the enthusiasm of the different observers. Such examples of therapeusis as cupping, blood-letting, balsams, baths, massage, metallic preparations and diets, as practised by early physicians have all repeatedly had their day of favor and decline through many centuries. One method, however, which has especially flourished and at times assumed an important role in the treatment of a rather wide field of disease is venesection. Although this method was held in universal esteem, there was never any agreement among practitioners as to the reasons for using it, the benefit derived from it or the technic. Hippocrates apparently used it with moderation. Galen, who loved to expound Hippocratic doctrines, wrote two treatises upon blood-letting. The Arabs introduced the theory of revulsion, which later stirred up the classic controversy between Brissot and the faculty at Paris. However, much these gentlemen may have quarreled among themselves concerning the theory underlying phlebotomy and the manner of administration, not one of them was heretical enough to discard it. It apparently never occurred to them to question the efficacy of the practice.

Yet having held sway for so long, it fell abruptly from its high estate during the middle of the nineteenth century. There seems to have occurred about 1850 a complete reversal of opinion among physicians and the general public which was the more remarkable because of the universal reliance upon blood-letting by a generation immediately preceding. From 1800 to 1840 there is a succession of papers which not only take the practice for granted but carry it to morbid lengths. Such examples of the freest possible use of leech and scalpel may be found in the works of Clutterbuck[1] and Wardrop.[2]

The feeling of resentment toward the practice of blood-letting in the seventeenth and eighteenth centuries and the deaths of several prominent men, such as Generals Washington and Harrison, naturally influenced the population in turning toward other methods of treatment. Until the time of Louis[3] no careful analysis had ever been made with a view of determining the exact value of bleeding

in definite conditions, taking into account the factors involved in previous treatment, the severity of the attack, the age of the patient and so forth. Louis came to the conclusion that the reliance placed on blood-letting was not justifiable. In discarding venesection as a method of treatment, however, the pendulum swung too far in the opposite direction. Bowditch,[4] about fifty years ago, realized this and in a paper in 1872, while deploring the evils of an earlier day, he mentioned a few cases which he had treated successfully by this method and believed that a rational use of venesection should be employed. For as he says it is recommended "in all acute cases where from any cause the heart apparently becomes distended with blood and consequently the circulation is greatly impeded, whereby orthopnea, lividity of the skin, with a very small and generally rapid pulse, mixed perhaps with other serious and disturbing symptoms, are produced."

It is difficult to estimate how often venesection is actually employed in general practice today, but its use in most hospitals may be said to be extremely limited. It has fallen away almost entirely in the treatment of infections and in certain diseases where the etiology was not previously known. In heart disease it is rarely used because of the satisfactory results obtained from such measures as rest in bed, theocin, digitalis, limitation of fluids, sedatives and so forth. However satisfactory the present treatment may be considered, the general disapproval and abandonment of venesection should not be unqualified in certain specific cases without critical study. That a certain well merited value in the treatment of the decompensated cardiac, for instance, has been overlooked and that actual revival may be in progress is suggested in a recent article by Christian[5] on the treatment of heart disease. He states that in marked cyanosis and its attendant dyspnea bleeding is often of great value, and that it is "far too little used at present in the management of the decompensated cardiac."

It is a common experience in speaking with practitioners, accustomed to analyze critically results of therapy, to have them state that certain patients, during severe forms of circulatory embarrassment, have responded dramatically to venesection. They have also admitted their failures, and in studying the unsuccessfully treated patients, consider their failures were due largely to the improper selection of cases for venesection or to the imperfect understanding of the limitations to which the procedure is subject.

Unfortunately, it is difficult to analyze a large series of patients with failure of the circulation, who have been subjected to pure venesection without the addition of other measures of treatment and to compare them with a like series of heart cases given well recognized therapeusis. The reasons are obvious. For instance, many patients receive such treatment before admission to the clinic that deductions as to the effect of venesection alone would be impossible.

Simple rest often produces surprisingly good results, where no medication has been given. If venesection were performed on a patient who was just on the verge of passing into a period of improvement as a result of previously administered therapy, it would be difficult to evaluate the exact part played by bleeding in the recovery. In studying the heart, such complications as fluid in the chest or the abdomen or cloudy lung fields have no doubt interfered with determining such factors as change in size and shape during the illness.

There has been, however, a steady flow of experimental evidence on certain features of the circulation. As far back as 1830 John Reed,[6] of Edinburgh, performed certain animal experiments which seemed to indicate an improvement in heart contractions after bleeding. Some attention has been given recently to the effect of bleeding on the size of the heart in animals. Eyster and Meek[7] and others have reported a moderate contraction of the heart following the withdrawal of venous blood amounting to about 2 per cent of the body weight. Although these observations have been made on animals with apparently normal circulation, they serve to emphasize what may be accomplished in human beings with acute dilatation of the heart.

Grant,[8] in some recent therapeutic studies in cardiac patients, found that the oxygen saturation of the venous blood was increased and the peripheral circulation improved after bleeding The striking clinical improvement in some of his patients aroused our interest in the possibility of demonstrating any immediate corresponding change in the size of the heart by roentgen ray as occurred in animals following venesection.[9] The problem was to determine what changes occurred in the size of the decompensated heart after venesection by roentgenography and to correlate if possible such changes, if they occurred, with certain clinical observations of the patient.

The technic employed was similar to that followed in a heart study by Cutler and Levine.[10] Briefly it consisted in placing the patient in a special bed which allowed the taking of roentgenograms at frequent intervals without disturbing the patient. The small series charted was selected from a group of 31 patients. The uncharted cases are those of the ascites and effusion group in which accurate measurements of the heart were impossible.

In the accompanying chart it will be found that 4 cases (Nos. 21032, 23894, 21929, 21191) showed a diminution in the size of the heart within a few minutes after venesection. In 2 instances there was a further reduction of these dimensions some time later. This was accompanied by a corresponding immediate improvement in the condition of the patient, strikingly so in 2 patients (Nos. 21032 and 23894). In 2 other patients (Nos. 21139 and 21192) there was a slight reduction in the outline of the heart but so small

as to be considered within the limits of error and there was no accompanying clinical improvement. These patients were all decompensated cardiacs but were free from abdominal and thoracic fluid except 1 (No. 21192), who had a moderate amount, not sufficient, however, to interfere with the obtaining of satisfactory roentgenograms. All patients, with the exception of 1 (No. 23894), who showed signs of serious heart failure, had spent a considerable time in bed and had been given various therapeutic measures before venesection was resorted to. In addition to this series there were 2 patients, 1 with hypertension and the other with hypertension and polycythemia, on whom venesection was performed. Although

ROENTGEN-RAY MEASUREMENTS OF THE HEART.

Hospital number.	Age.	Diagnosis.	Amount of blood withdrawn.	Time elapsed between venesection and taking of roentgenograms.	Transverse diameter of heart.	Immediate clinical result from venesection.
21191 . .	71	Chronic myocarditis, auricular fibrillation	550 cc.	A. .. B. 10 min. C. 30 min. D. 50 min.	17.4 17.5 16.6 16.1	Improved
21139 . .	23	Chronic cardiac valvular disease	500 cc.	A. .. B. 20 min. C. 55 min.	18.6 18.8 18.4	Unimproved
21929 . .	60	Chronic myocarditis, auricular fibrillation	600 cc.	A. .. B. 48 min.	18.2 17.2	Improved
21192 . .	44	Chronic cardiac valvular disease, auricular fibrillation, chronic passive congestion of the liver, ascites	500 cc.	A. .. B. 40 min.	15.4 15.0	Unimproved
23894 . .	58	Chronic myocarditis, arteriosclerosis	900 cc.	A. .. B. 20 min. C. 90 min.	20.9 19.6 18.8	Greatly improved
21032 . .	80	Chronic myocarditis	500 cc.	A. .. B. 45 min. C. 90 min.	18.5 17.6 16.2	Greatly improved
21364 . .	51	Hypertension	550 cc.	A. .. B. 45 min.	13.0 12.5	Improved
21448 . .	62	Polycythemia, hypertension	550 cc.	A. .. B. 28 min. C. 2 hours.	16.4 16.8 16.6	Improved
W. W. .	24	Normal	450 cc.	Control 20 min.	11.5 11.5	Unchanged
S. C. . .	23	Normal	500 cc.	Control 18 min.	14.3 14.4	Unchanged
F. M. . .	26	Normal	450 cc.	Control 35 min.	16.5 16.3	Unchanged
D. W. . .	35	Normal	550 cc.	Control 25 min.	13.4 13.2	Unchanged

A. = Roentgenogram taken before venesection.
B. and C. = Roentgenograms made following venesection.

here there was definite clinical improvement, the heart did not diminish in size. Four other patients, who were normal individuals so far as known and who were bled as donors for transfusion, also showed no change in the heart. In studying this group due consideration was given to the position of the diaphragm as suggested by Williamson,[11] Bordet [12] and others. In all instances the measurements of both the chest and diaphragms corresponded in the films of the same individual.

This series, although necessarily small because of the difficulty of studying patients severely ill and of obtaining satisfactory roentgenograms, suggests that in some cases a diminution in the size of the decompensated heart occurs a short time after venesection with an accompanying striking clinical improvement of the patient. Just what physiological adjustment develops in the failing heart as a result of phlebotomy is open to speculation. It may be assumed that because either a considerable load has been removed from the circulation or the viscosity has been reduced by the transfer of fluid from the tissues, the heart is able to more easily perform a function within its capacity, and thus develop an improved muscle tone. It would seem therefore that a failing heart becomes more efficient when extreme dilatation is reduced to a moderate dilatation. Cases which showed no improvement may come in the group of individuals with hearts so physiologically unresponsive except to the demands of the body at almost complete rest that tonicity and the powers of recuperation may be considered as practically negligible. The possibility that actual fatigue may be playing a part in dilatation is suggested by the fatigue which develops in the voluntary muscle with an insufficient blood supply. Wearn[13] has reported some preliminary studies on the diseased hearts of adults which suggests that during dilatation there is a decrease of the blood flow through the capillaries of the heart. If this be true, it is possible that undernutrition and certain anatomical alterations develop various toxic substances in the myocardium which are improperly removed, and cause these hearts to be unresponsive to venesection. As Hewlett[14] remarks, "the heart muscle may have become fixed in the new position so that even though strain be relieved or the muscle weakness disappear, the ventricle remains permanently larger than before."

The explanation for the absence of the diminution in heart size in the hypertension cases was probably due to either an insufficient amount of blood being withdrawn or to the absence of dilatation other than what was physiological. The same reasons may also explain the failure of obtaining a change in the heart in the normal individuals.

In order to get some idea of the feeling of house officers on the value of bleeding a number of records extending from 1914 to 1924 were reviewed. The impression received from the history notes is for

the most part enthusiastic about the immediate temporary improvement. Not a few notes suggest that the patient's life was actually saved by the procedure. In others there is a feeling of skepticism which suggests that bleeding accomplished no more than other less bothersome methods would have done. This latter sentiment is mentioned occasionally between many periods when venesection was quite freely used. How much this was due to the actual feeling that bleeding could be easily dispensed with or how often the proper subject for bleeding was admitted to the clinic was impossible to decide but there is a striking similarity to the periodic waves of bleeding that occurred in past centuries. In the hospital records, however, there is no evidence that blood-letting was employed to any great extent except on the decompensated cardiac, the hypertensive and occasionally in pneumonia. Quite satisfactory results from a purely symptomatic standpoint have been obtained in the hypertensive patients. The headaches, throbbing, dizziness have frequently been removed with striking rapidity although there has been only a slight temporary lowering of the blood pressure. A number of the decompensated heart patients have also received great symptomatic improvement, especially those with dyspnea, cough, restlessness, and the appearance of suffocation and cyanosis. Pulmonary edema is mentioned as being relieved considerably after venesection. Although relief in the cardiac group has not always been prolonged, it has, however, in many instances, been sufficient to carry the patient along while other measures were brought into play. There is one point which seems to be emphasized not infrequently in the history notes, and that is, where no beneficial effect was obtained from venesection, other procedures have also failed including the use of cardiac drugs and general stimulants.

The following cases are examples which serve to illustrate the immediate effect of venesection. They were taken from house-officers notes and are a part of the patients' record while in the Peter Bent Brigham Hospital. M. C., Med. No. 4303, male, aged thirty years. Diagnosis: Chronic myocarditis, chronic valvular heart disease and chronic nephritis. The patient had been in the hospital for several days under treatment. A note by Dr. S. A. Levine reads as follows: "The patient had considerable pain under the right costal margin evidently from a distended liver. He was bled 800 cc. which gave him considerable relief. Just before bleeding the edge of the liver was easily palpable a hand's breadth below the costal margin. It was pulsating. A short while after the bleeding was completed the edge was about two fingers below the costal margin and it was not tender."

C. W., Med. No. 16706, female, aged forty-five years. Diagnosis: Chronic myocarditis, hypertension, peripheral arteriosclerosis, acute uremia. This patient had been in the hospital for one day

before the following note was written by Dr. E. S. Emery: "For the first twenty-four hours in the hospital the patient seemed to be doing fairly well. She was rather stuporous but had no complaint and remained quietly in bed. On the evening of the second day she suddenly complained of shortness of breath. She was breathing very rapidly and shallowly and was deeply cyanotic. The pulse was rapid and rather weak. She gave the appearance of a patient in acute decompensation. Morphin was given which quieted her but she became extremely cyanotic, respirations were rapid and the pulse could hardly be obtained at the wrist. A phlebotomy was done with the withdrawal of 900 cc. Whether due to the treatment or not, she improved rapidly after bleeding, the cyanosis disappeared, breathing became easier and slower and the patient said she felt much better."

F. W. C., Med. No. 24767, aged fifty-seven years. Diagnosis: Infarct of the heart, angina pectoris, hydrothorax. Admission ten days before venesection. A note by Dr. R. B. Wilson is as follows: "Tonight about 10 o'clock the patient became extremely dyspneic, pulse being rather feeble, skin cold and clammy and rather markedly cyanotic. Following the venipuncture the patient felt immediately very much improved, the cyanosis disappeared, the pulse improved, the skin became warm, perspiration disappeared and the patient went to sleep in about twenty minutes, apparently greatly improved as the result of the bleeding."

Summary. The roentgenographic examination of a series of decompensated hearts in patients with failing circulation showed a diminution in the size of the heart immediately after venesection. When this occurred, there was a corresponding improvement in the condition of the patient. It is suggested that the hearts in these cases are more efficient in a moderately dilated form than when extremely dilated. In those cases, where no changes in the heart size occurred, it is felt that the muscle tone was so unresponsive to venesection because of certain anatomical changes in the myocardium that no improvement occurred in the circulation. A survey of the hospital records shows that numerous patients, bled as an emergency measure after other procedures of therapy such as drugs had failed possibly because of their delayed action, responded favorably to venesection. It seems, therefore, that venesection has a place in improving the action of the decompensated heart and temporarily at least in removing signs and symptoms of failure.

I wish to express my appreciation to Drs. Albert Wilmaers and Guy Wells and numerous house officers for their help in carrying out the study and to Dr. M. C. Sosman and Dr. E. S. Emery, Jr., for many helpful suggestions.

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MICROCYTOSIS IN HEMOLYTIC ICTERUS.

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In 1898 hemolytic icterus was first established as a clinical entity by Hayem.[1] He stated that, aside from the types of chronic jaundice caused by obliteration of the bile duct or compression by tumor and by hypertrophic biliary sclerosis, there were other types of the disease that were but little understood. He then described 5 cases of icterus with very large spleens and a marked chronic anemia, the red cells varying in number from 2,493,000 to 632,000 per cu.mm., and he classified this variety as of a markedly hemolytic type (une maladie fortement déglobulisante) with crises of varying intensity and duration. Bile pigment was present in the blood serum, but not in the urine, and the itching and clay-colored feces, found in other types of icterus, were lacking. He proposed to name the disease "chronic infectious splenomegalic jaundice of a paroxysmal type."

In 1907, Chauffard,[2] after eight years of study and research, described some cases of familial hemolytic jaundice with microglobulia and a greatly weakened cellular resistance, as shown by

the fragility test. He observed that the average diameter of the red cells was between 5 and 6 microns and that polychromatophilia and granular degeneration of the red cells were present. In this type of icterus the liver merely plays a passive part, serving as an organ of reception, transformation and insufficient elimination of the superabundant products and it is the spleen in reality that plays the preponderant part in this disease. Chauffard regarded hemolytic jaundice as a "noli me tangere" for the surgeon.

In 1900, Otto Minkowski[3] published his studies of hemolytic icterus describing it as "a hereditary disease characterized by chronic icterus with urobilinuria, splenomegaly and renal siderosis," and the disease showed an anomaly in the destruction of the blood pigment subordinate to a primitive lesion of the spleen.

This hemolytic jaundice appears to be due to an excessive fragility of the red corpuscles, which, on liberating the hemoglobin, furnish the material for the production of jaundice. Here the resistance of the red cells to hypotonic sodium chlorid solutions is lowered, while in obstructive jaundice, pernicious anemia and splenic anemia the resistance of the red cells is increased.

In this disease there is no obstruction of the bile passages, but the spleen becomes greatly enlarged and filled with red corpuscles. According to William J. Mayo[4] the spleen in the adult, like other organs of the reticulo-endothelial system, has for one of its proper functions the destruction of deteriorated red cells. When the spleen is enlarged as from splenic anemia or hemolytic icterus, this destruction may become excessive and produce the chronic anemia, leading to death directly, or indirectly through intercurrent disease.

One characteristic anatomical feature of this disease, seen on examination of the stained blood film, is the great majority of microcytes among the red cells. Evidences of active attempts at regeneration are also seen, such as polychromatophilia, and nucleated red cells, most of them normoblasts.

Naegeli,[5] in his 1923 edition of "Blutkrankheiten und Blutdiagnostik," in discussing hemolytic jaundice regards these microcytes as belonging to a peculiar type of red corpuscles, which is inherited. He concludes that these inherited microcytes indicate a distinct type of human species.

While these red cells appear abnormally small they show an apparent increase of the hemoglobin content in each cell, while in secondary anemias from tumors, nephritis and in hemorrhage, and in chlorosis where large numbers of microcytes are found, the cells are much paler than normal. In fact, it is evident that these cells show, by their increased hemoglobin content, an approach to an actual spherical form instead of the normal biconcave or cup-shaped disk form.

Meulengracht investigated Naegeli's theory of the relation of microcytosis and its heredity to hemolytic jaundice and found that

the blood type was transmitted only by members of the family having the disease, the children of those unaffected being normal in this respect.

The question in regard to this microcytosis is this: Is it simply a characteristic symptom of the anemia in hemolytic icterus influenced to a large extent by the condition of the spleen and disappearing after splenectomy, or is Naegeli's statement true that the microcytosis is an intrinsic feature of this disease? In case the latter be true, we must expect that splenectomy would not change this abnormality of the red cells.

During the past three years I have been studying the blood conditions before and after splenectomy in some of these cases of hemolytic icterus, and during the past year a more detailed research has been made of the microcytosis and a decrease and subsequent general disappearance of the microcytes has been observed.

One cannot make an accurate decision in regard to this question by mere visual inspection of the red cells in the stained film and therefore exact measurements have been made of the cells before and after splenectomy by the following method. A series of successive fields in each particular slide was projected on paper by means of an Edinger apparatus, with measurements of a micrometer scale projected at the same focus. Outline drawings were made of the red cells in each projected field. Each cell was numbered, and its measurements were taken with a small pair of dividers and compared with the projected micrometer scale, and by this method 200 cells in each slide were measured.

Three of these cases of hemolytic icterus occurred in the same family, the mother and two small boys being affected.

Case Reports. CASE I.—Mrs C. W., gave a negative family history for this disease. She first noticed intermittent attacks of jaundice after her first labor, with loss of appetite, distaste for food and occasional nausea, but no vomiting. She was admitted to the Fordham Hospital on March 10, 1922, poorly nourished in her general appearance, with pinched facies and greenish-yellow complexion. No blood transfusion was given.

On March 16, splenectomy was performed by Dr. E. R. Cunniffe, the condition having been diagnosed as Banti's disease. The patient made an excellent recovery and was discharged from the hospital on March 30. Her jaundice disappeared, her general physical condition improved and within six weeks she had gained 15 pounds.

Blood Counts. The first blood count taken on March 14, 1922, showed a moderate degree of anemia (Table I) with some microcytosis of the red cells. A count taken on May 6, about six weeks after splenectomy, showed some general improvement in the blood findings and two subsequent blood counts taken at the Fordham

Hospital on October 9, 1922, and January 19, 1924, showed improvement in the blood picture, especially the latter. On May 15, 1924, she came to the surgical clinic of the Post-Graduate Hospital and a complete blood count was taken. This, and a later one on January 3, 1925, showed a return to normal.

TABLE I.—COMPARISON OF BLOOD COUNTS TAKEN FROM MRS. C. W. (CASE I) PREVIOUS TO AND FOLLOWING SPLENECTOMY, SHOWING A RETURN TO A NORMAL BLOOD PICTURE.

	Red cells.	White cells.	Gms. Hgb.	Differential count (per cent).								Platelets.
				Pol.	S. L.	L. L.	Mon.	Tr.	Eos.	Bas.	Mye.	
3/14/1922 . .	3,000,000	5,400	10.5									
3/16/1922 Splenectomy												
5/ 6/1922 . .	4,060,000	9,400	10.5									
10/9/1922 . .	4,000,000	18,400	14.6	78	22							
1/19/1924 . .	4,900,000	10,000	16.3	68	6	22		1	1	1		
5/15/1924 . .	4,304,000	7,200	13.4	60	18	14	2	2	1	1		
1/6/1925 . .	4,392,000	8,200	13.8	57	10	18	7	3	4	1		

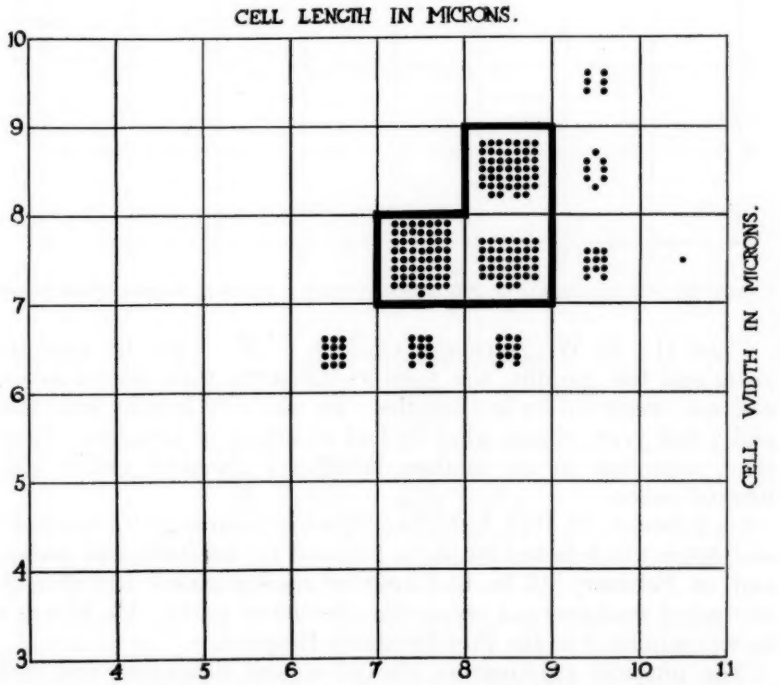

CHART I.—Measurements of 200 erythrocytes in a blood smear taken from Mrs. C. W. (Case I) two years and eight months after splenectomy. In this and the following charts the squares containing the cells of normal size (7 x 7, 7 x 8 and 8 x 8 microns) are bounded by heavier lines,

Microcytosis. No measurements were made of the patient's cells previous to her operation, but the cells in the smears taken on January 6, 1925, were measured and found to be quite normal in size (Chart I). For comparison measurements were made of the red cells in a smear of normal blood (Chart II).

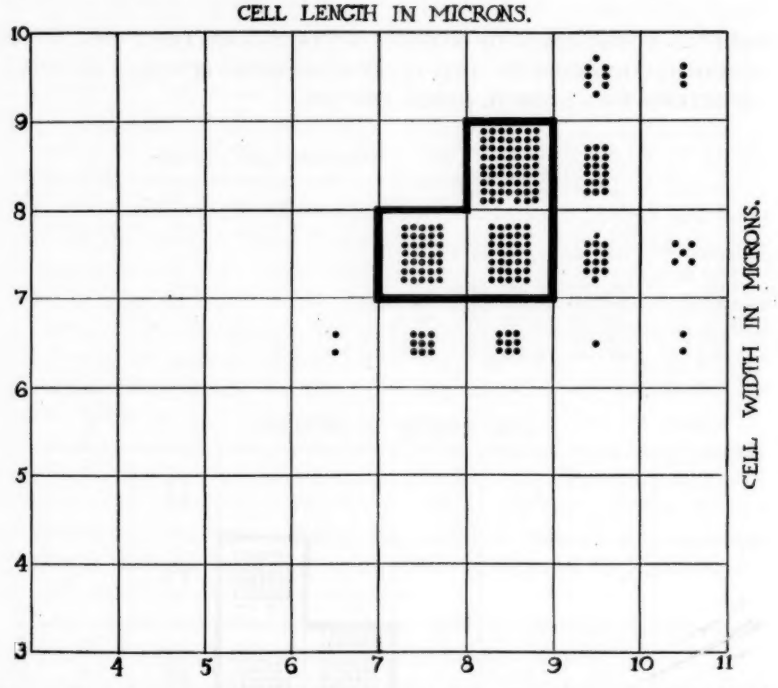

CHART II.—Measurements of 200 erythrocytes in a smear of normal adult blood.

CASE II.—R. W., older son of Mrs. C. W. (Case I), aged six years and two months, was born at full term, with normal labor, and was breast fed for ten months. He was very healthy until two and a half years of age, when he had an attack of jaundice. Since then, according to the mother, he always appeared yellow with marked pallor.

On February 16, 1924, he had an attack of vomiting with headache and fever which lasted ten days, followed by lassitude and pallor, and on February 28 he had another similar attack followed by increasing weakness and cramp-like abdominal pains. On March 6 he was admitted to the Post-Graduate Hospital.

The physical examination showed a well developed and well nourished boy, with a yellow-tinged skin. The abdomen was not distended, but hypersensitive on palpation, and painful on percussion. The liver edge was palpable just below the costal margin and the spleen palpable for two finger breadths below.

The Wassermann test was negative.

TABLE II.—COMPARISON OF BLOOD COUNTS TAKEN FROM R. W. (CASE II) BEFORE AND AFTER SPLENECTOMY, SHOWING A RETURN TO A MORE NORMAL BLOOD PICTURE FOLLOWING THE OPERATION.

	Red cells.	White cells.	Gms. Hgb.	Differential count (per cent).								Platelets.
				Pol.	S. L.	L. L.	Mon.	Tr.	Eos.	Bas.	Mye.	
3/ 6/1924 . .	1,034,000	8,000	3.4	83	3	8	3	2			1	
3/12/1924 Transfusion, 500 cc.												
3/18/1924 . .	3,200,000	5,000	8.9	59	16	11	4	5	4			153,000
3/20/1924 . .	3,488,000	6,400	8.5	70	10	9	4	4	2	1		
3/21/1924 Splenectomy												
3/28/1924 . .	3,408,000	5,000	10.4	50	19	10	16	1	4			
5/15/1924 . .	4,190,000	7,000	10.5	50	30	10	7	1	1	1		
1/6/1925 . .	4,384,000	8,200	12.9	52	31	11	4		2			

Blood Counts. The first blood count taken on admission showed a marked anemia (Table II) with polychromatophilia and granular degeneration. During the differential count 3 normoblasts and 3 microblasts were found. On March 12, the patient was transfused with 500 cc. of blood, and a count taken on March 18 showed a great improvement, especially in the number of red cells and amount of hemoglobin.

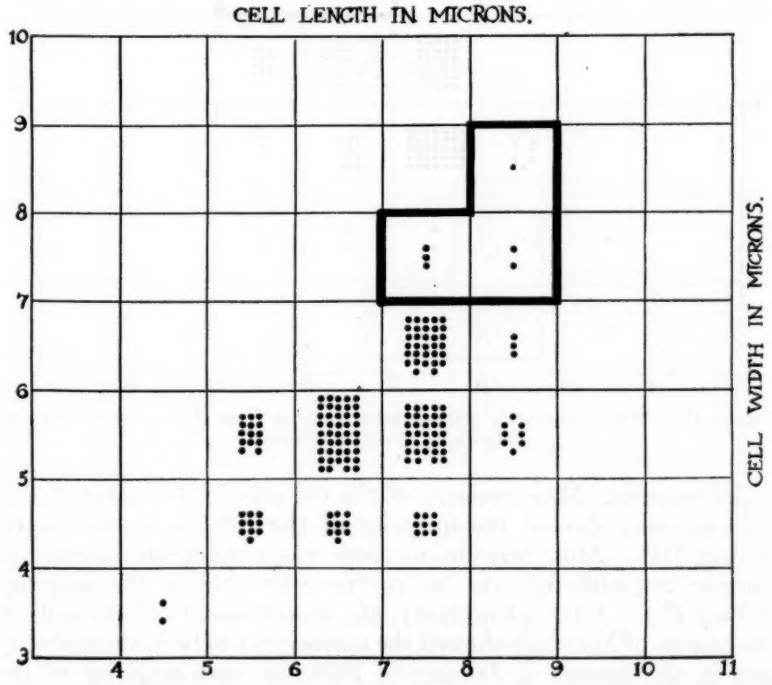

CHART III.—Measurements of 200 erythrocytes in a blood smear of R. W. (Case II) taken at time of admission to the Hospital on March 6, 1924. Note the small number of normocytes.

Splenectomy was performed on March 21 by Dr. J. F. Erdmann from which the patient made an excellent recovery, and on April 13 he was discharged.

The first blood count taken after the operation showed but little change in the cell count from that of March 20, but another count taken on May 15, when he was brought to the surgical clinic, showed a return to a more normal blood picture.

He was seen again on January 6, 1925, and was found to be in excellent general health, having had no illness since his discharge and he showed a healthy rosy color. The blood count showed quite a normal picture.

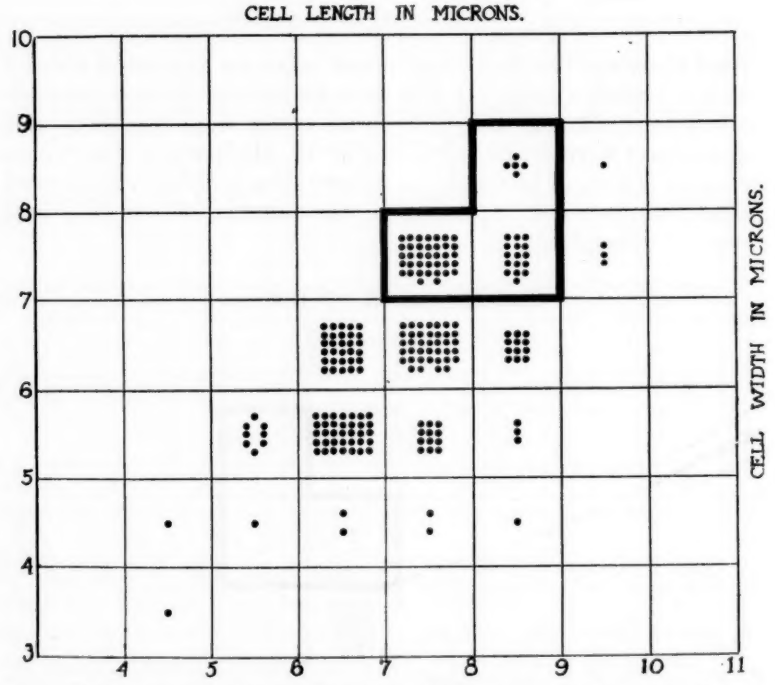

CHART IV.—Measurements of 200 erythrocytes from Case II in a smear taken on March 20, after transfusion.

Microcytosis. Measurements of the red cells in the smears taken on admission showed the majority of the cells to be microcytic (Chart III). After transfusion there was a moderate increase of normocytes, although the microcytes were still in the majority (Chart IV). After splenectomy, the measurements of the cells in the smears of March 28 showed the normocytes to be in the majority and in the smears of January 6, 1925, the vast majority of the cells were of normal size, and the microcytes very few in number (Chart VI).

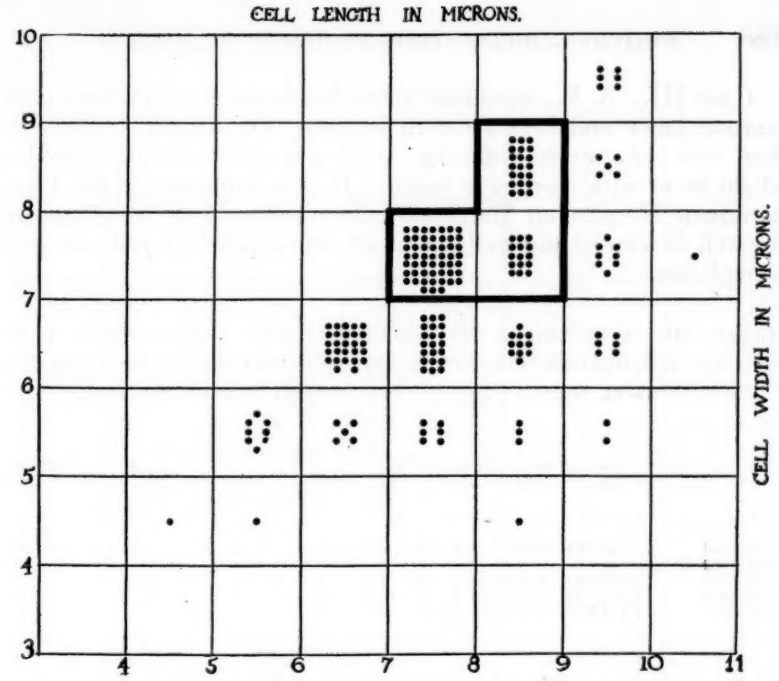

CHART V.—Measurements of 200 erythrocytes from Case II, in a smear taken a week after splenectomy, showing a return of the cells to a more normal size.

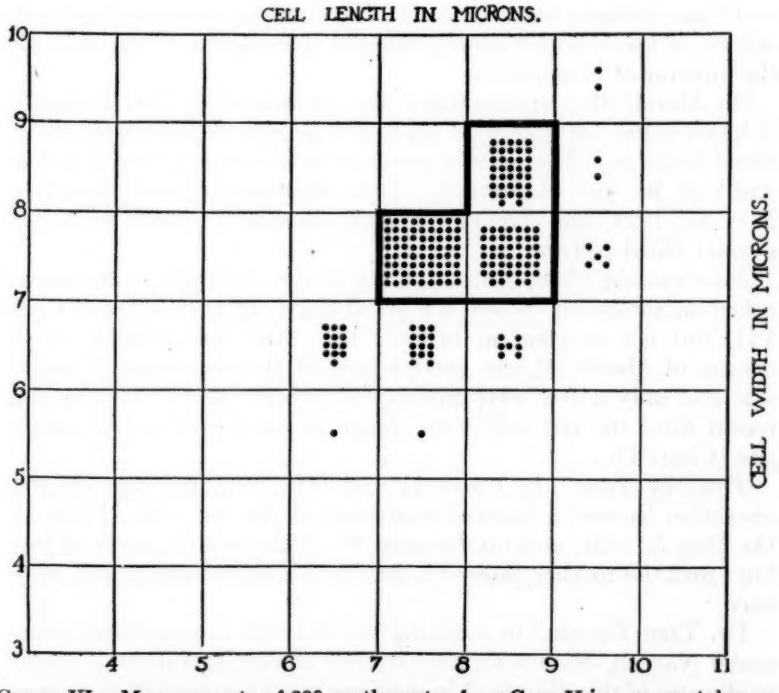

CHART VI.—Measurements of 200 erythrocytes from Case II in a smear taken on January 6, 1925, showing the vast majority of cells as of normal size.

CASE III.—A. W., aged four years, brother of Case II, born with normal labor and breast fed in infancy. On March 9, 1924, he had two very severe vomiting spells and afterward developed a slight fever with increasing pallor. He was admitted to the Post-Graduate Hospital on March 17. On examination he was found to be well developed and well nourished with a pale and yellow-tinged complexion.

TABLE III.—COMPARISON OF BLOOD COUNTS TAKEN FROM A. W. (CASE III) BEFORE AND AFTER SPLENECTOMY SHOWING A RETURN TO A NORMAL BLOOD PICTURE FOLLOWING THE OPERATION.

	Red cells.	White cells.	Gms. Hgb.	Differential count (per cent).								Platelets.
				Pol.	S. L.	L. L.	Mon.	Tr.	Eos.	Bas.	Mye.	
3/17/1924 . .	1,736,000	10,600	5.4	67	17	11		5				136,000
3/21/1924 Splenectomy												
3/29/1924 . .	3,640,000	6,200	10.2	65	11	9	7	2	4	2		
5/15/1924 . .	4,208,000	5,800	10.2	41	21	26	5	1		1		
1/6/1925 . .	4,416,000	9,000	13.4	61	27	10	1		1			

Blood Counts. The blood count on admission showed a marked anemia with many polychromatophilic and stippled red cells (Table III). During the differential count 13 normoblasts, 6 microblasts and 6 macroblasts were seen. On March 19 he was transfused with 400 cc. of blood which nearly doubled the number of red cells and the amount of hemoglobin.

On March 21 a splenectomy was performed by Dr. Erdmann. A blood count on March 29 showed a general improvement in the blood findings. The patient made an uneventful recovery and on April 13 he was discharged. Two subsequent blood counts of May 15, 1924, and January 6, 1925, showed a return to a good normal blood picture.

Microcytosis. The measurements of the red cells in the smears taken on admission showed a marked degree of microcytosis (Chart VII) but not as great as in Case II. After splenectomy, in the smears of March 29, the greater part of the cells were of normal size and only a few were microcytic (Chart VIII). In the most recent films the red cells were shown to have returned to normal size (Chart IX).

Fragility Tests. In Cases II and III a fragility test prior to operation showed a lowered resistance of the red cells (Table IV) On May 5, 1924, and on January 10, 1925, fragility tests of both boys and the mother showed a return to a fairly normal cell resistance.

Dr. Taro Toyada,[6] in studying the red cells in congenital icterus under Naegeli, discusses a microcytosis of varying intensity present in all cases of this disease. These microcytes have no della but appear

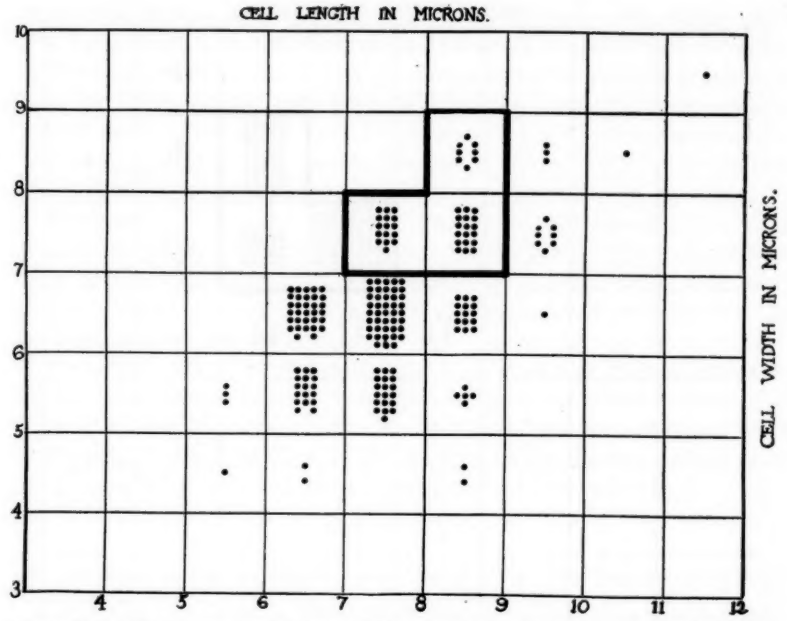

CHART VII.—Measurements of 200 erythrocytes in a blood smear of A. W. (Case III) taken at date of admission to hospital.

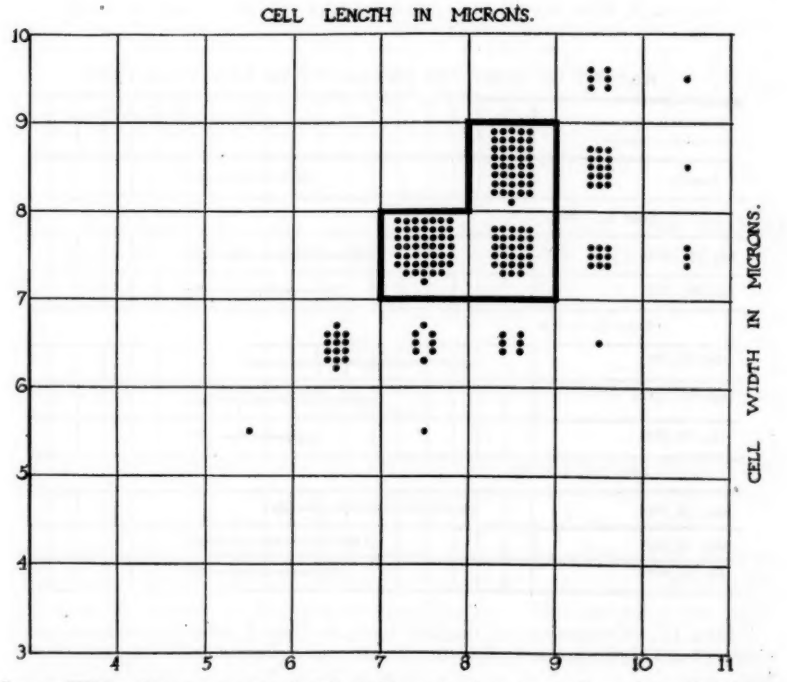

CHART VIII.—Measurements of 200 erythrocytes in a smear from Case III taken after splenectomy on March 29.

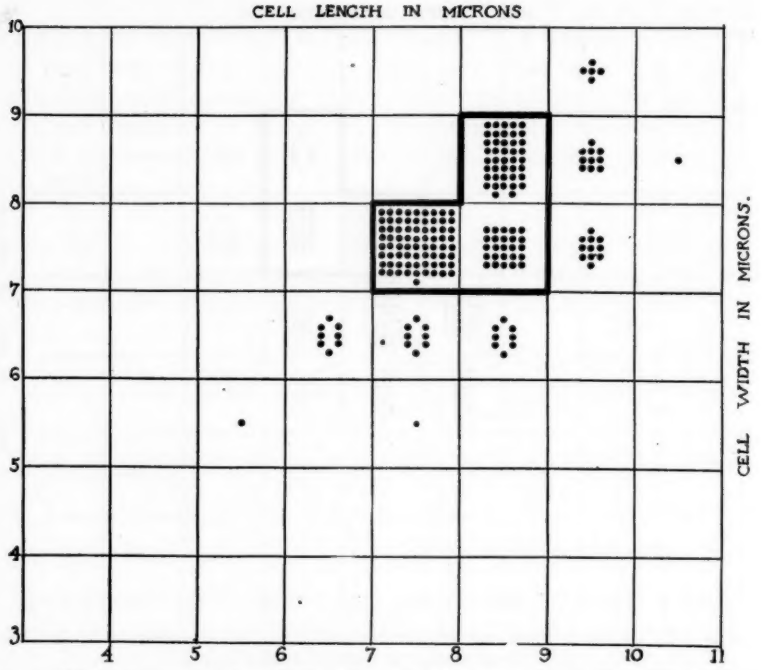

CHART IX.—Measurements of 200 erythrocytes in a smear from Case III taken on January 6, 1925, showing the greater part of the cells as normal in size.

REPORT ON TEST FOR FRAGILITY OF ERYTHROCYTES

Calculated percentage of Sodium Chloride	.855	.810	.765	.720	.675	.630	.585	.540	.495	.450	.405	.360	.315	.270	.225	.180	.135	.9
Normal									I●				●C					
Case I. - Mrs. C.W.																		
May 15, 1924							I●						●C					
Jan. 10, 1925								I●					●C					
Case II. - R.W.																		
Mar. 18, 1924			I●								●C							
May 15, 1924							I●						●C					
Jan. 10, 1925									I●				●C					
Case III. - A. W.																		
Mar. 20, 1924			I●								●C							
May 15, 1924							I●						●C					
Jan. 10, 1925								I●					●C					

TABLE IV.—Comparison of fragility tests, in Case I after splenectomy and in Cases II and III before and after the operation as compared with a normal fragility test.

somewhat more intensely stained than normal cells, while cells 8 to 12 microns in size are usually pale and often polychromatophilic.

Toyada measured the red cells in a number of smears from patients with this disease and thereby found that in most of the splenectomized cases there was a marked decrease or total disappearance of the 4 and 5 micron cells, some decrease of those of 6 microns and an increase in those of normal size.

Summary. According to these studies of the blood pictures in hemolytic icterus before and after splenectomy, there is shown, from careful measurements of the red cells, to be a return to a more normal blood picture and a very distinct improvement in the corpuscles after the operation.

Therefore, because of the disappearance of the microcytes after splenectomy in contrast to their abundance in the blood in hemolytic icterus before the operation, this feature may be regarded as a concomitant manifestation of the anemia of the disease, rather than an inherent character of the erythrocytes of the individual.

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THE MAGNESIUM AND CALCIUM CONTENT OF THE BLOOD AND BLOOD PLASMA OF TUBERCULOUS PATIENTS.*

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This paper contains some observations regarding the magnesium content of the blood of normal people and people with pulmonary tuberculosis; it also gives the calcium content of the blood.

The calcium content of the blood serum has been the subject of extensive investigations in recent years, not only in tuberculosis, but also in other pathological conditions. The reasons for pub-

* The author wishes to acknowledge much personal assistance from Dr. L. Dienes whose methods and modifications were used.

lishing this relatively small series are: That the results were obtained with a different method from that ordinarily used and because the magnesium content is given as well. The great stability of the calcium content of the blood serum, the relation of the calcium values in the blood to certain pathologic conditions and the influence of the parathyroid glands in regulating the calcium content of the blood seem to be well established. Although there is not sufficient material to give us much idea as to the significance of magnesium in the blood, even a small series obtained by reliable methods seem to be not without interest. The remarkable consistency of both the calcium and magnesium values point to the possibility that even small variations in the values in different individuals can be the sign of important constitutional characteristics. Our purpose was rather to collect material to characterize the tuberculous individuals, to see if it would be really possible to find constitutional characteristics of them, rather than to obtain more insight into the disease.

The question of the methods used in the analytical work is very important. For instance, the method of De Waard for the determination of calcium which has been used quite extensively in Europe is (according to the seemingly valid criticism of Hirth and Klotz[1]) not appropriate even for approximate comparative determinations. The method used by us, both for the calcium and magnesium determinations, is one recently described by L. Dienes.[2] The determinations are made after ashing the organic material, and the method is equally well applicable to blood and serum. The accuracy of the method is high; the parallel determinations usually agree to $\frac{1}{1000}$ mg. Two modifications were made in the original procedure: (1) In the precipitation of iron and phosphorus the weighing of the tubes was discontinued and readings were made of the volume in graduated tubes instead (using a tube 9 to 10 mm. in diameter and a volume of 1.25 cc., the error does not exceed 1 to 2 per cent); (2) in the same way, in precipitating the calcium, the tube was weighed only after pipetting off the oxalate solution. The amount of the solution was determined by the volume.

The accuracy of the method was somewhat influenced by the first modification, but no constant error was made by it and the technic and calculations were simplified.

Both the calcium and magnesium determinations were made on the blood and blood plasma, the plasma being obtained by centrifuging the cooled blood. For controls the red blood cell residue was also analyzed which, together with the values obtained from the plasma, enables one to calculate the values for the whole blood.

In the table containing the results of our work there are given, in addition to the classification of cases, some data on the constitutional characteristics, such as age, stature, state of nutrition

TABLE I.

Normal Cases all in Good Health and Good Nutrition	Calcium milligrams in 1 cc.		Magnesium milligrams in 1 cc.	
	Blood.	Plasma.	Blood.	Plasma.
F. K., 23 years; tall, slender, 137 lbs.	0.053	0.093	0.032	0.020
F. L., 22 years, medium build, 145 lbs.	0.052	0.092	0.033	0.022
E. S., 28 years, very tall, 195 lbs.	0.050	0.093	0.031	0.018
Mrs. F., 25 years, fairly tall, 145 lbs.	0.057	0.095	0.030	0.020
J. F., 33 years, medium, 170 lbs.	0.055	0.096	0.032	0.021
L. D., 38 years, medium, 142 lbs.	0.050	0.089	0.032	0.018
Mrs. S., 43 years, short, 135 lbs.	0.051	0.086	0.033	0.019
R. F., 46 years, tall, 165 lbs.	0.044	0.088	0.033	0.024
Miss B., 45 years, tall, 150 lbs.	0.052	0.096	0.039	0.026
Tuberculosis Cases—*Incipient*				
Mr. Y., 38 years, tall, slender, improving nutrition, 150 lbs, normal temperature, now apparently well	0.043	0.079	0.032	0.021
Mr. B., 38 years, tall, slender, improving nutrition, 148 lbs, normal temperature, now much improved	0.048	0.075	0.037	0.024
Mr. H., 30 years, medium height, improving nutrition, 125 lbs., normal temperature, now apparently well	0.046	0.084	0.037	0.022
Mrs. H., 29 years, short stature, nutrition good, 110 lbs., normal temperature, now apparently well	0.051	0.083	0.032	0.025
Moderately Advanced				
Mrs. D., 36 years, tall, slender; improving nutrition, 112 lbs., normal temperature, now improved	0.046	0.080	0.033	0.023
Mrs. M. D., 21 years, medium height, 133 lbs., nutrition good, massive empyema, right thorax drained, normal temperature, now apparently well	0.045	0.085	0.035	0.020
Mr. B., 37 years, tall, slender, 130 lbs., nutrition improving, normal temperature, now improved	0.039	0.074	0.036	0.025
Mr. T., 39 years, tall, slender, 141 lbs., nutrition improving, normal temperature, now improved	0.044	0.086	0.029	0.020
Miss H. L., 30 years, tall, slender, 103 lbs., nutrition poor, but improving; temperature 99°, now improved	0.047	0.080	0.031	0.023
Mrs. C., 28 years, tall, slender, 123 lbs., nutrition improving, normal temperature, now very much improved	0.052	0.095	0.032	0.021
Mr. S., 35 years, tall, stout, 171 lbs., nutrition good, normal temperature, now very much improved	0.048	0.097	0.029	0.021
Advanced				
Mrs.T., 24 years, tall, thin, 93 lbs., nutrition poor, temperature 99°+, now unchanged	0.048	0.082	0.039	0.025
Mr. C., 30 years, tall, thin, 138 lbs., nutrition poor, temperature 100° to 101°, now unimproved	0.053	0.077	0.033	0.020
Mrs. G., 41 years, medium height, 100 lbs., nutrition poor, temperature 99°, now unimproved	0.052	0.086	0.031	0.021
Mrs. M., 41 years, medium height, 128 lbs., nutrition fairly good, temperature 100° maximum, now improved	0.050	0.085	0.032	0.025

and weight. The calcium values in the normal cases are a little lower than are usually found with the Kramer and Tisdall method and are considerably less than those obtained by the method of De Waard, which gives values with human serum that are too high according to Hirth and Klotz. Our normal values are very close to those found by the method of Hirth and Klotz[3] (0.086 to 0.105 mg. in the plasma), which method also ashes the organic material first. Our values in pathologic cases are decidedly less than found by other workers, but this may be caused by chance, as the series is small. We are not inclined to attribute much importance to our findings in the tuberculous cases until they are better controlled by the same method. The determinations of the normal cases were made in a distinct series at a different time.

The magnesium values in the normal cases are very similar to those published by Kramer and Tisdall,[4] and Salvesen and Linder,[5] using Kramer and Tisdall's method, and the values published by Briggs.[6] They are also similar to those of Blum and Klotz,[7] determined after ashing the blood plasma (0.023 to 0.027 mg. per cubic centimeter of plasma). The range of variations is quite considerable from 0.018 to 0.026 mg. per cubic centimeter of plasma and 0.031 to 0.036 mg. in the whole blood. The same range of variations was found in the tuberculous patients. With our small material it was impossible to find any connection between the constitutional appearance of the individuals examined or their pathologic condition and the amount of blood magnesium. But the considerably greater variability of the magnesium content of the blood as compared with the calcium content makes an extensive study of them desirable. As the red blood cells contain more magnesium than the plasma, the determination of the magnesium not only in the plasma but in the blood also is necessary.

In recent years Walbum[8] has observed that the intravenous injection of different inorganic salts can raise considerably the antibody production; he has even reported experiments according to which the resistance of experimental animals infected with tubercle bacilli can be raised by the intravenous injection of manganese salts. Of the salts which are very effective in the raising of antibody production it is only the magnesium which occurs in large quantity in the blood (besides traces of manganese). According to the conception of Walbum, the action of the salts is catalytic, accelerating the formation of antibodies, or it may be a stimulus of the reticuloendothelial system by the colloidal precipitate which is formed by the intravenous injection of the salts. The chemical individuality of the precipitate has a decisive influence. This observation gives a new interest to the study of the magnesium and was partly the reason we have undertaken it.

Summary. In normal and tuberculous individuals a variation of the magnesium content of the blood plasma was found between 0.018 to 0.026 mg. per cubic centimeter and 0.031 to 0.038 mg. in the whole blood. No connection with the pathologic condition or the age, stature and body weight was found. The calcium values in the blood plasma of normal persons determined after ashing it proved similar to the values found by others, using a similar method, but were found considerably less in the blood plasma of tuberculous patients.

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THE NONTUBERCULOUS PULMONARY FIBROSES.

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Since the recent epidemics of influenza numerous articles have appeared on the subject of the subacute and chronic pulmonary infections of nontuberculous origin. The outstanding features of these papers are the lack of details as to the exact pathology and the indiscriminate use of the words "unresolved pneumonia," "chronic interstitial pneumonia" and "pulmonary fibrosis." It was hoped that further light could be thrown on these conditions from a pathologic standpoint, but unfortunately it is difficult to obtain material since these cases do not usually progress to a fatal issue.

The following classification will suggest the wide range for study provided by this subject but in this paper discussion will be limited to the first group, with brief remarks concerning the others under the differential diagnosis:

Types of Pulmonary Fibrosis. 1. Following the acute respiratory infections.
2. Tuberculosis.
3. Syphilitic.
4. Pneumokoniosis.
5. Following exposure to war gases.
6. Fungus infections.

The problem is an important one, both economically and medi-

cally, for by recognizing the etiology and preventing the contributory factors a large amount of the resulting disability can be eliminated. From the standpoint of the child, at which age the incidence of this disease is greatest, much time lost from school could be prevented. With a more careful differentiation of cases in the adult many would escape the stigma of being labeled tuberculous, to say nothing of the economic saving by keeping them out of sanatoria. That this latter factor is important may be seen from the following statistics. Rist,[1] in his clinic at the Laënnec Hospital, Paris, found 62 per cent of the cases referred to him as tuberculous to be suffering from nontuberculous diseases. Many had been treated for long periods of time as tuberculous. Funk[2] states that out of 1200 consecutive cases referred to the tuberculosis wards of the Jefferson Hospital, Philadelphia, 6 per cent were nontuberculous. Stivelman[3] in an analysis of 1700 consecutive admissions to a tuberculous sanatorium found 176 suffering from nontuberculous infections. Of these, 12 had chronic interstitial pneumonia, 10 had bronchiectasis, 11 had nontuberculous lung disease not definitely classified but suggestive of fibrosis.

A review of the literature dates back to the article by Corrigan,[4] in 1838, in which he laid emphasis on the nontuberculous nature of a case of fibrosis and described the process of formation of bronchiectatic cavities by the shrinkage of the interstitial fibrous tissue. He labeled the condition "cirrhosis of the lung" and was the first to call attention to the displacement of the heart and other organs of the mediastinum.

In 1894 the first extensive work appeared on the subject written by Clark, Hadley and Chaplin.[5] This contains a complete bibliography up to that date, from which the following points were extracted. Ivergensen and Rokitansky[6] were the first to describe an interstitial inflammatory process and gave it the name of "interstitial pneumonia." Eustace Smith[7] thought the process occurred in the interlobular tissue and in the alveoli as well. Clark, Hadley and Chaplin[5] discuss the pathology in detail stating that it is both an interstitial and an intraälveolar process and therefore refuse to accept the term interstitial pneumonia. They compare a series of tuberculous and nontuberculous cases, emphasizing the good nutrition in the latter group, the absence of fever in association with a normal pulse rate, and a chronic cough and expectoration.

Jacobi[8] in an article on interstitial pneumonia describes it as one of the three types of pneumonia occurring in infancy and childhood. He believes it may occur as a sequela of the other pneumonias or as an independent disease occurring then most frequently in the right upper lobe and running a protracted course with fever for weeks or even months. Recovery is rarely complete, induration and retraction of the pulmonary tissue with bronchiectasis being frequent complications. He considers it a pulmonary hyperplasia,

with secondary fibrosis. The bibliography contained in this paper gives references to the important articles up to 1903.

Miller[9] reviews the literature up to 1917 and reports on a series of 22 cases seen, which he divides into 3 groups: (1) The subacute type; (2) subacute type with recurrences, and (3) the chronic type. In this classification and in the articles reviewed by him there are examples of cases which went on to complete recovery (that is, probably so called unresolved pneumonias) and others in which there was a continuance of physical signs and symptoms, and which had undoubtedly developed a permanent fibrosis and even bronchiectasis. However, there is no definite classification on an etiologic or pathologic basis. The bacteriologic reports given show a predominance of the following organisms, in the order of their frequency: Pneumococcus, Type IV; B. influenzæ and Streptococcus viridans.

Lord[10] states that in a study of 85 cases of bronchopneumonia with autopsy no relation could be made out between the causative organism and the persistence of pulmonary signs and symptoms.

Riesman[11] discusses a lobar form of bronchopneumonia of long duration, occurring in children and young adults which clears up without residue and without evidence of retraction. The course of the disease extends from weeks to several months. It is commonest in the second decade and seems to predominate in girls.

Recently Packard[12] has called attention to the predominance of pneumonias of mixed type in recent years. Those due to the streptococcus and B. influenzæ are largely lobular and tend to have the inflammatory exudate organized rather than resolved. He notes also the frequent formation of many small abscesses. Signs of unresolved pneumonia occur most commonly, according to him, at the angle of the scapula.

Symmers and Hoffman[13] call attention to the increased incidence of organizing or unresolved pneumonia "which is anatomically and clinically distinct from the chronic interstitial pneumonia of syphilis, tuberculosis and the like since the connective-tissue replacement is almost exclusively confined to the intraälveolar spaces." This condition occurs according to them in a certain proportion of all cases of lobar pneumonia.

Louis Hammon,[14] in the section on Diseases of the Lungs in *Oxford Medicine,* divides chronic pulmonary inflammatory conditions into:

1. Pulmonary cirrhosis, induration or fibrosis.
2. Secondary chronic inflammatory disease.
3. Primary chronic inflammatory disease.

He then goes on to say "secondary chronic inflammatory disease of the lungs, or as it is often called, chronic pneumonia, is usually a step on the way to cirrhosis. Unresolved lobar pneumonia is the commonest cause . . . Bronchopneumonia may be followed by a similar train of events."

Frequent attention is called in the literature to the importance of upper respiratory infections as a contributory factor in the disease. Field[15] states that the frequency of mouth breathing and chronic nasal disease in children increases the liability to bronchial disease. He believes another predisposing factor in childhood is the relatively large amount of loose connective tissue in the walls of the bronchi and alveoli which is easily invaded by the infecting organism. He found B. influenzæ most common, with the streptococcus and staphylococcus next in order. He suggests that dilatation of the smaller bronchi occurs early in the disease, as shown by the tendency to paroxysmal cough with large amounts of sputum.

Dunham and Skavlem[16] point out that in 389 cases sent to the radiographer as possible pulmonary tuberculosis 18 had unresolved basal bronchopneumonia. These they considered were secondary to the following infections: Influenza 10; infected antra 3; infected frontal sinus 1; infected ethmoids 4.

Pierson[17] also notes the importance of chronic upper respiratory infections, generally sinusitis, in connection with chronic pulmonary disease.

Hebert,[18] who says that nontuberculous fibrosis is the commonest chronic pulmonary disease of childhood, points out the early age at which the process starts. He places the onset usually in the second or third year, following whooping cough or measles with bronchopneumonia, but finds that clinically the condition is not diagnosed until the child is eight or nine years of age. In his experience (personal communication) the unresolved pneumonias differ from pulmonary fibrosis usually in history and clinical course. The former come in children, generally after influenzal pneumonia or in adults after lobar pneumonia. The latter come after the bronchopneumonias of childhood, usually complicating measles and whooping cough. This is a persistent thing, going on usually to bronchiectasis. The unresolved pneumonias lose their symptoms in four to six months and repeated roentgenographs over a year or two show a gradual clearing of the dense area.

Very little is offered in the literature concerning treatment. Miller[9] advises a dry climate and the removal of all nasal sinus infections. For those who have gone on to bronchiectasis he advises drainage by the inverted posture.

Jacobi[8] believed the iodids were of value in early cases in which the hyperplasia had not gone on to cirrhosis. He recommended treatment with the drug over long periods of time.

Pierson[17] suggests more radical measures. For early cases within six months of the onset and before extensive fibrosis has developed he would advise artificial pneumothorax. For those which show rapid progressions of the fibrosis and have large bronchiectatic cavities he advises thoracoplasty. In support of these radical measures is the frequency with which cerebral abscess and other septic con-

ditions occur as a complication of bronchiectasis (see postmortem statistics).

The present study covers a series of 30 cases personally seen in the wards and outpatient departments of several London hospitals and sanatoria. It includes a review of 1000 consecutive postmortems at the City of London Hospital for Diseases of the Chest and 1000 at the Hospital for Sick Children, Great Ormond Street, in which is seen the low incidence of fibrotic lung conditions.

TABLE I.—REVIEW OF 2000 POSTMORTEMS.

Diagnosis.	City of London Hospital.	Hospital for sick children.	Total.
Pure fibrosis	0	1	1
Fibrosis plus bronchiectasis	16	2	18
*Bronchiectasis	13	3	16
Tuberculous fibrosis	7	1	8
Tuberculous fibrosis with bronchiectasis	9	2	11
	45	9	54

* Three cases of bronchiectasis secondary to mediastinal tumors and aneurysm were omitted.

TABLE II.—COMPLICATIONS.

Diagnosis.	Fibrosis and Bronchiectasis.	Tuberculous fibrosis.
Bronchopneumonia	2	6
Lobar pneumonia	2	0
Cerebral abscess	4	0
Septic meningitis	1	0
Pericarditis	2	0
Pyopneumothorax	2	0
Empyema	4	3
Gangrene	3	0
Tuberculous peritonitis	0	1
Miliary tuberculosis	0	3
Total	20	13

Several interesting facts are brought out in these tables, the most important of which is that pure fibrosis without any accompanying bronchial dilatation is seldom seen in the postmortem room. Table II shows the high incidence of septic complications in the nontuberculous group.

In the 2 groups there was a total of 18 children, 10 of whom had nontuberculous fibrosis and 8 tuberculous fibrosis. Of those over fifteen years of age, 27 were nontuberculous and 10 tuberculous. In this connection it is interesting to quote Hebert[18] who says: "In adults the relative frequency of the two types of fibrosis is reversed and only prolonged investigation can justify the diagnosis of nontuberculous fibrosis." This is not in accord with the postmortem figures given above, but it is undoubtedly true clinically. The discrepancy may be accounted for by the fact that most of these children survive to adult life.

Pathological Findings. GROSS. At postmortem these cases show a contracted lung which is tough and cuts with more resistance than normal. Small sections from densely fibrotic areas do not float in water. The pleura is usually thickened and often the lung is bound down by old adhesions. The hilum glands are usually enlarged moderately but show no caseation. On section there is present in practically all cases a varying degree of bronchial dilatation, greatest at the bases and frequently associated with small abscess cavities. (Fig. 1.)

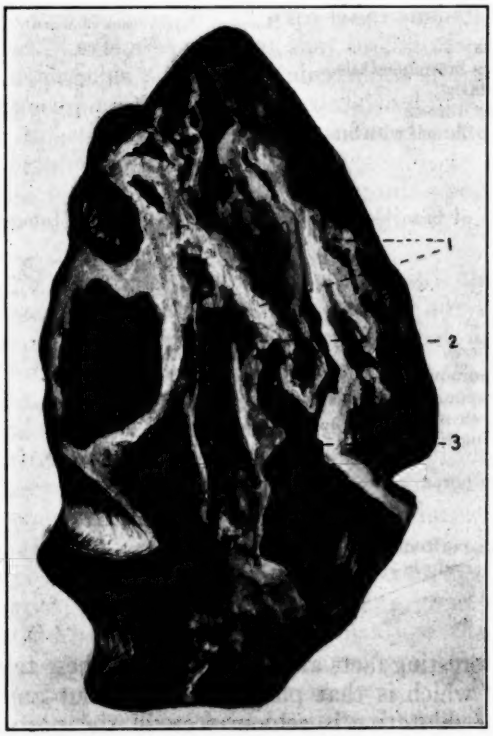

FIG. 1.—Section of fibrotic lung. 1, Fibrous tissue; 2, bronchus; 3, abscess cavity.

MICROSCOPIC. In the early stages there is an increased vascularity with the invasion of the tissues by lymphoid cells. Later one sees the development of elastic tissue fibers in the interalveolar spaces and around the bronchi and bloodvessels. Finally there is an obliteration of large areas of alveolar tissue, an absence of bloodvessels and the gradual contraction of the fibrous tissue. Coincident with this contraction there is a dilatation of the bronchioles and bronchi, due to the strain put upon their walls by the shrinkage of the adjacent tissue. Any inflammatory process going on in the

walls of the bronchi themselves undoubtedly aids this process. The columnar cells of the bronchial mucosa are often missing and there is a piling up of the cells of the basement membrane. (Fig. 2.)

It is regretted that no sections of early unresolved pneumonia could be obtained, but reference is again made to the article by Symmers and Hoffman[13] who call attention to the fact that in these cases the process is intraälveolar and not interstitial, as in fibrosis.

ETIOLOGY. The frequency with which nontuberculous fibrosis occurs in childhood may be judged from the following fact: Out of 1000 consecutive admissions to the outpatient department at The Hospital for Sick Children, Great Ormond Street, 15 were diagnosed as having a nontuberculous fibrosis or unresolved pneumonia.

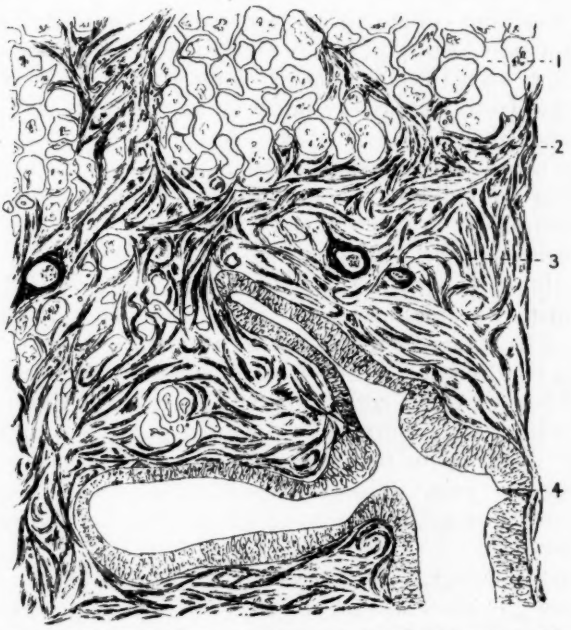

FIG. 2.—Section of fibrotic lung. × 1080. 1, alveolar tissue; 2, fibrous tissue invading interalveolar space; 3, bloodvessels surrounded by dense fibrous tissue, 4, dilated bronchus.

In the 30 cases studied there were 20 children (between eighteen months and fourteen years of age) and 10 adults (ages nineteen to fifty-seven). In 14 of the 20 children the onset of the disease occurred during the first five years, the remainder between five and ten. In 7 the condition could be directly traced to a preceding whooping cough which was severe and usually associated with bronchopneumonia. Six dated their symptoms to pneumonia, of unknown etiology; and in 2 it followed a severe attack of chicken pox. Measles, although said to have aggravated a preëxisting

chronic bronchitis, was never given as the immediate precursor of the illness. In 5 children the exact relationship to previous infections was not known but in each case there was a history of repeated severe respiratory infections.

Among the adults the connection with preceding respiratory infections was equally definite. Of the 10 cases, pneumonia was the primary factor in 4. In 3 it was traced to influenza, in 2 the preliminary infection was undecided although there was a history in each case of repeated respiratory infections. One followed gassing with phosgene.

In all the cases there was a history of possible exposure to tuberculosis in only 4 cases.

SYMPTOMATOLOGY. The outstanding feature in all these cases was the recurrent cough, always worse in the winter. The children gave a constant history of loss of time at school but the adults were able to carry on with their work. The cough was productive, usually only with a fresh respiratory infection and often ceased entirely in the summer time. Those having the clinical signs and roentgen-ray evidence of bronchiectasis had a more copious expectoration but among the children the sputum was seldom foul and never in large amounts.

Dyspnea was more common in the adults but was never severe. Pain in the chest was not a common symptom. Eleven patients gave a history of night sweats. Hemoptysis and streaking of the sputum each occurred 4 times. Pulse and temperature were normal.

Among children in a healthy environment and with sufficient food (Cases I to IV) the general nutrition was good. But the average child coming to the outpatient department of the large hospitals was very much below par. They gave a history of wasting or of very irregular gain. They did well in convalescent homes but immediately lost on return to the city, and usually picked up a fresh infection.

Physical Findings. APPEARANCE OF THE CHEST. Contraction or flattening of the chest on the affected side is an important sign, occurring in 18 of the 30 cases. It usually involves the whole side of the chest and, when marked, is associated with scoliosis. Occasionally the flattening was limited to the supra- and infraclavicular spaces when the original process had been a localized unresolved lobar pneumonia. Diminished expansion, with poor air entry on the affected side, usually occurs but is sometimes difficult to determine in children.

DISPLACEMENT OF THE MEDIASTINAL ORGANS. One expects to find with the process of shrinkage going on in the lung tissue, a displacement of the moveable viscera. Marked displacement of the heart is easily determined but where it is slight one is apt to overlook it. Confirmation with the roentgen ray is important. In the 30 cases displacement of the heart occurred 18 times. The

frequency with which displacement of the trachea occurs in tuberculous fibrosis is commonly used as a differential point (owing to the more frequent involvement of the apices) but in this series it occurred in 7 of the 23 cases rayed and considered to be nontuberculous.

PERCUSSION. The normal resonance of the chest is impaired on the affected side and is most marked, usually, in the lower two-thirds. In cases which have developed bronchiectatic cavities the dullness of course varies with the amount of retained secretion. Emphysema occurred in the adults but was seldom found in the children.

AUSCULTATION. These have been described by some writers as the "noisiest chests" one can listen to. But the sounds vary a great deal from time to time and, in fact, when no associated bronchiectasis is present the pure fibrotic chest often has diminished breath sounds with no rales. More often there is bronchovesicular breathing or a type of squeaky leathery breathing which is quite characteristic of marked fibrosis. Over dilated bronchi, tubular or amphoric sounds occur. Rales, when present, are large and moist and frequently have a metallic note. In the early unresolved pneumonias signs of consolidation are found, usually over a fairly circumscribed area. As the process clears the dulness, bronchial breathing and moist rales give place to moderate impairment, diminished breath sounds with a bronchovesicular character, and fewer rales. From this stage the findings depend upon whether the process undergoes complete resolution or progresses to fibrosis.

ROENTGEN RAY FINDINGS. The Roentgen ray findings show in most cases the following definite features: On the affected side the chest is contracted and by comparing the two sides of the plate one sees a diminished costochondral angle and narrow interspaces. With the fluoroscope, expiration is limited and the ribs on that side are seen to lag. The roentgen ray is particularly valuable in determining the presence and amount of mediastinal displacement which involves especially the heart but may also include the trachea and bronchi. In the lung fields the important points are a peribronchial thickening, extending particularly toward the bases, and a diffuse dilatation of the smaller bronchi which may be clearly seen as circular outlines varying in size from a millet seed to a pea. There is a varying degree of opacity present and emphysema may be seen in other parts of the lung.

VON PIRQUET. Since the need for diagnosis of these conditions comes largely during childhood the von Pirquet reaction is valuable. In the Vienna clinics a negative von Pirquet reaction is sufficient evidence to class a child as nontuberculous and this absolute reliance can be well understood when one sees how thoroughly the Viennese are able to check up their clinical findings by postmortem examination.

Lemon[19] believes that flattening and immobility of the diaphragm are not sufficiently emphasized in the diagnosis of fibroid disease.

CLUBBING. Clubbing of the fingers is an important sign and should lead one to suspect bronchiectasis. In the 14 cases complicated by bronchiectasis it occurred in 6 children and 5 adults. In those who had no signs of bronchiectasis it was present in 2 children and 1 adult. It must not be forgotten that clubbing occurs in the toes as well as the fingers.

LABORATORY FINDINGS. It is regretted that owing to the variety of places from which this material was collected a greater uniformity of the routine laboratory work was impossible. The character of the sputum and a study of its bacteriology are important. As a rule the sputum, when present, is white and mucoid in contrast to the yellow or greenish purulent sputum of tuberculosis. In infancy, where sputum is not easily obtained, because it is swallowed, examination of the feces is advisable. A repeatedly negative sputum is good evidence that the condition is not tuberculous.

In those cases in which the sputum was cultured, the predominating organisms were the pneumococcus and streptococcus, which agrees with the statistics of other authors.

Course of the Disease and Prognosis. If one could definitely differentiate the more or less generalized process of fibrosis from the pneumonias with delayed resolution, it would be less difficult to picture the course of the disease. In general, one may say that the unresolved pneumonias show their maximum amount of clearing (best determined by the roentgen ray) within twelve to fifteen months after the onset. Any residue after this length of time is usually permanent and undergoes fibrosis. As a rule these cases become symptom free in four to six months after the acute illness.

Those patients having fibroid changes ultimately go on to bronchiectasis because of the shrinkage of the fibrous tissue and consequent dilatation of the bronchi. The relatively bad prognosis when this stage is reached may be seen from a study of the septic complications shown in the postmortem table. Probably few of those whose infection can be traced back to childhood live beyond forty-five years of age. Of the 35 nontuberculous fibroses obtained from the series of 2000 postmortems, 7 died in the first decade, 4 in the second, 5 in the third, 8 in the fourth and 11 in the fifth decade. The prognosis can be greatly influenced by the environment of the individual and freedom from fresh infections.

TREATMENT. In the treatment of the nontuberculous fibroses drugs are probably only palliative, although Jacobi's[8] suggestion concerning the use of iodids is worth a thorough trial. In early cases breathing exercises are of definite value in helping to expand the chest, and the use of the Woulfe bottle is recommended.

Emphasis cannot be placed too strongly on the importance of a suitable environment in an equable climate, where they are free

from respiratory infections. It is particularly important to see that children are allowed to completely recover from their epidemic infections associated with bronchial involvement. The temptation to let children up, because of the difficulty in keeping them in bed, before the temperature and physical signs have returned to normal, undoubtedly plays its part in the development of these chronic lung conditions. All foci of infection, such as the tonsils, adenoids, and sinuses, should be thoroughly searched for and eradicated.

Pierson's[17] views on the radical treatment of these cases has been gone into. It is of interest here to note that Davies[20] gives his mortality following thorocoplasty as 8.3 per cent and quotes Gravesen, and Jacobaeus and Key as having a mortality of 8.6 per cent and 8 per cent respectively. Brauer[21] believes that with properly selected cases the mortality should not be over 2 per cent.

Differential Diagnosis. The separation of the nontuberculous from tuberculous fibroses is the most important problem in the differential diagnosis. A repeatedly negative sputum is the most valuable criterion but next in importance comes the history, dating back to a previous respiratory infection, the relatively mild character of the symptoms with a great tendency to recurrent cough. The pulse and temperature keep below the level usually found in tuberculosis and the amount of disability is not in proportion to the physical findings. The location of the lesion is important, for it is usually basal in the nontuberculous cases. In tuberculosis where there is a similar amount of basal involvement one will find at some time in the history of the case more marked constitutional symptoms, and the response to rest and improved hygiene is not so marked. The occurrence of hemoptysis does not necessarily point to the diagnosis of tuberculosis. It is produced by the erosion of vessel walls by secondary invading organisms and this can occur in either type of case.

The roentgen ray is a valuable adjunct. It is important to look for such evidence of tuberculosis as Ghon's "primary focus" which appears as a small calcified area usually well out in the lung fields, and the secondarily involved lymph glands which may or may not be calcified. The characteristic "fuzzy" opacities of tuberculosis are not seen. The presence of bronchial dilatation is in favor of fibrosis while true cavitation points to tuberculosis. The greater displacement of the upper mediastinal organs in the tuberculous type is again helpful but not conclusive, as shown by the cases given.

Clubbing may occur in both conditions but is more common in the nontuberculous fibroses which have gone on to bronchiectasis.

In childhood, use should be made of the von Pirquet test.

Case XXX is included in this series since it offers a difficult problem from the standpoint of the differential diagnosis. With the history of exposure to infection and other manifestations of

tuberculosis one feels justified in calling the lung lesion tuberculous. On the other hand, the excellent nutrition does not seem compatible with such an extensive tuberculous process in the lung. The presence of a positive von Pirquet reaction of the bovine type may help to explain the low toxicity of the process. Case XXXI is also interesting from the diagnostic standpoint. One would be inclined to discount the one and only positive sputum, found thirty-one years ago, and consider the case a nontuberculous fibrosis were it not for the great number of calcium deposits throughout the lung fields. This patient is further evidence of the greater disability and poorer nutrition occurring in the tuberculous type, in contrast to the nontuberculous. Simple chronic bronchitis can usually be differentiated by the fact that the signs are more widespread and the rales do not have the coarse, moist, consonating quality of a fibrosis.

The question will often arise as to whether one is dealing with an unresolved pneumonia or an empyema. Points in favor of the former are the absence of a septic temperature and sweating. The leukocyte count tends to be higher in empyema although cases are seen in children in which a leukopenia persists. The roentgen-ray picture is more dense with fluid and with the fluoroscope one fails to get a clear space on deep inspiration below the opacity as one does with consolidation. By thorocentesis one should be able to settle the question.

The differentiation from a syphilitic fibrosis must depend primarily on the Wassermann reaction and the therapeutic test. Evidence of other syphilitic lesions is helpful. Funk[2] states that fibroid lesions of this character referred to syphilis do not possess any cardinal characteristics and cannot be distinguished during life from fibrosis due to tuberculosis and other causes.

Pneumokoniosis may proceed for years without giving any symptoms and may only be diagnosed when found by Roentgen ray or at autopsy. The more serious kinds such as silicosis, however, produce the physical signs of fibrosis and give rise in time to serious symptoms. The differential diagnosis depends on the history of exposure to dust inhalation, the diffuse nature of the lesions and the disproportionate amount of dyspnea with good general health. In the later stages the symptoms become more severe than in the type of nontuberculous fibrosis discussed in this paper. The Roentgen ray is of definite value in these cases since it shows the fine peppering throughout the lung fields with the inorganic particles.

That fungoid growths in the lungs may be a source of confusion in the diagnosis will be seen from the statement of Lord,[22] in *Oxford Medicine*, to the effect that the thoracic form of actinomycosis is next in frequency to the abdominal type. He says "the abundance of connective-tissue formation is a striking feature and is responsible for the contraction of the affected side." The diagnosis here rests on finding the typical organisms in the sputum.

Case XXIX is included as an example of the difference between fibrosis subsequent to gassing and that following the respiratory infections. The excellent nutrition, marked dyspnea, sense of constriction in the chest and the fine tracery of the roentgen-ray shadow are all characteristic and in definite contrast to the other forms of fibrosis.

Case Reports. Following is a series of cases taken from the 30 studied, which illustrate the points brought out:

Case XV.—Male, aged ten years. Diagnosis: Nontuberculous fibrosis; bronchiectasis. The family history is negative, with no known exposure to tuberculosis. The past history included left unresolved pneumonia at two years of age; measles at three; whooping cough at eight. The child has had a chronic cough since the pneumonia at two, and aggravated by whooping cough. Physical examination shows an undernourished child with clubbing of the fingers, which has been present since the age of two. There is slight contraction of the left chest but no displacement of the mediastinal organs. The percussion note is impaired throughout the left chest, especially at the base where there are harsh breath sounds and moist rales. The Roentgen ray shows marked fibrosis of the left chest with dilated bronchi. The sputum was repeatedly negative for tubercle bacilli, with the pneumococcus predominating. The pulse and temperature were normal.

Case XVI.—Male, aged eighteen months. Diagnosis: Bilateral nontuberculous fibrosis; bronchiectasis. The family history is negative. Past history includes chicken pox at eight months, with persistent cough ever since, and wasting for the past three months. Physical examination shows an undernourished child with slight clubbing. There is a Harrison's groove and poor expansion of the chest. On percussion, there is impairment of resonance throughout both chests posteriorly and at the left base there are signs suggesting a cavity. The roentgen ray shows marked peribronchial thickening and dilatation of the bronchioles. There is no evidence of infiltration. The von Pirquet was negative. The sputum was negative 8 times for tubercle bacilli, with the streptococcus and pneumococcus being the predominating organisms. The pulse and temperature were normal.

Case XXIX.—Male, aged thirty-seven years. Diagnosis: Gas fibrosis. The past history is essentially negative. The present illness began at the age of twenty-eight, when he was gassed with phosgene. Since then he has complained of tightness of the chest, dyspnea, cough and sweats. There is a small amount of sputum, which was streaked once. Physical examination shows an over-

weight man with slight cyanosis and no clubbing. The chest expansion is very poor. The percussion note is hyperresonant throughout and the breath sounds are bronchovesicular, with many musical rales. There is no displacement of the mediastinal organs. In the Roentgen ray the bronchioles appeared dense but fairly well defined, and there was a fine web-like tracery of diffuse fibrosis throughout both lung fields. The sputum was negative for tubercle bacilli 8 times. The pulse and temperature were normal.

CASE XXX.—Female, aged fifteen months. Diagnosis: Unresolved pneumonia; fibrosis; pulmonary tuberculosis. The patient's father died of pulmonary tuberculosis when the baby was two months old. The past history includes bronchopneumonia at five months, with fever for one month, lupus (?) at nine months, tuberculous dactylitis at fifteen months. The present history is that of chronic cough since the bronchopneumonia at five months. Physical examination shows a well-nourished child with slight contraction of the right chest. The percussion note is impaired over the entire right chest and the upper third of the left. The breath sounds are harsh over the left and distant on the right. There are no rales. A series of Roentgen rays showed gradual clearing of a pneumonic process in the right lung and upper third of the left, with the heart displaced to the left. There was questionable evidence of activity at the left apex. The sputum was negative for tubercle bacilli but the von Pirquet test gave a marked positive reaction with the bovine tuberculin. The pulse and temperature were normal.

CASE XXXI.—Female, aged seventy-one years. Diagnosis: Tuberculous fibrosis with excavation. The patient's father and one brother died of tuberculosis. The past history includes "inflammation" of the lungs at twenty-five and influenza at forty-six. She has had a chronic cough since she was twenty-five, with an hemoptysis at sixty-three and seventy. Her present symptoms are dyspnea, giddiness and weakness. Her sputum was positive for tubercle bacilli at the age of forty but has been repeatedly negative ever since. Physical examination shows the patient is very poorly nourished, with poor chest expansion and supra- and infraclavicular flattening. There is impaired resonance over the right upper and middle lobes, and to a less extent on the left. There are signs of a cavity at the right apex and crepitant rales and bronchial breathing at the left. The Roentgen ray showed masses of calcareous material throughout both lung fields, with signs of cavitation at the right apex. The pulse and temperature are normal.

Summary and Conclusions. An attempt has been made in this paper to bring out: (1) The salient points in the differentiation of

the nontuberculous fibroses; (2) the course and sequelæ of chronic pneumonic processes; (3) their prevention and treatment.

In the differential diagnosis the question of tuberculosis is of paramount importance. Here the history of the case, the general conditions of the patient, the von Pirquet reaction and Roentgen-ray picture are the determining factors.

The chronic pneumonic lesions of the lung can be divided from the clinical standpoint into 2 groups: one is the socalled unresolved pneumonia and the other chronic pulmonary fibrosis. Of the first, a certain proportion will entirely clear up in six months to a year while the others go on to a permanent fibrosis. But a large proportion of the group of pulmonary fibroses is made up of cases which have developed insidiously after whooping cough and bronchopneumonia without showing a definite stage in which one could say that resolution had failed to take place.

These primary infections occur usually in early childhood but the condition is not diagnosed until varying degrees of bronchiectasis have supervened.

Because of the long-standing disability, prophylaxis in these cases is exceedingly important. It can best be accomplished by removing sources of exposure to whooping cough and measles and, more particularly, by seeing that the lung has returned to normal after these infections before the child is discharged. When there is a residual lesion the case must be carefully followed by repeated Roentgen ray and physical examinations. In these cases it is especially important to remove all foci of infection both in the individual and his environment and to improve his general hygiene.

The treatment is largely palliative during the acute exacerbations. All sinus or throat infections should be carefully searched for and cleared up. In cases with extensive unilateral lesions and bronchiectasis, artificial pneumothorax, as advised by Pierson,[17] has to be considered. Where collapse is impossible, owing to adhesions, one has to carefully weigh the seriousness of the symptoms and dangers from septic complications against the fairly high mortality attendant upon the more radical operations.

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A STUDY OF FOUR HUNDRED AND FIFTY CASES OF EPIDEMIC ENCEPHALITIS.*

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Introduction. The present outbreak of epidemic encephalitis seems to have started in Vienna in the winter of 1916 and 1917. Since that time an enormous literature has developed in continental Europe, England and the United States.

In this paper no effort will be made to review this literature, as our object is simply to present the outstanding features that have developed in the study of a rather large number of cases.

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These cases were seen beginning in the fall of 1918 and during the following five years up to 1924. The 1924 cases, 81 in number, have not been included, as we wish to emphasize somewhat the after effects of encephalitis and it is still too early to report on the sequelæ of these cases.

In the fall of 1918 we first realized that we were beginning to see cases of a type that was new to us. Since 1910 the meningitis division has been studying cases of meningeal involvement, the different kinds of meningitis, poliomyelitis, meningism occurring in the various acute infections and other rarer conditions involving the central nervous system. This experience gave us a fairly good background on which to study this interesting disease.

At first we did not recognize that the cases were epidemic encephalitis. We were misled by the reports in the English literature, that the spinal fluid findings were negative, and also by the fact that the English reported that the cardinal symptoms were lethargy, asthenia and cranial nerve palsies. With rare exception, the spinal fluids in our cases have not been normal. While the triad of symptoms described by the English is very characteristic when present, many cases do not present all three and some not even one of these symptoms. As time has passed it has been recognized more and more that cases of epidemic encephalitis present a widely varied symptomatology. The term encephalitis lethargica seems to us very unfortunate, since it emphasizes a symptom which is frequently not present. It is very difficult to convince a patient or his family that he has encephalitis lethargica when insomnia and restlessness are the outstanding symptoms.

The following, Tables I, II and III, show the distribution of cases by year, season, sex and age:

TABLE I.—DISTRIBUTION BY YEARS AND SEASONS.

Year.	Jan. Feb. Mar.	Apr. May, June.	July, Aug. Sept.	Oct., Nov., Dec.	Total.
1918 . . .	0	0	1	10	11
1919 . . .	26	4	9	29	68
1920 . . .	65	19	11	16	111
1921 . . .	49	25	25	9	108
1922 . . .	18	34	8	11	71
1923 . . .	45	17	14	6	82
Total . .	203	99	68	81	451

From the above table it will be seen that the greater number of cases occur in the first three months of the year and the smallest number in the summer months.

TABLE II.—DISTRIBUTION AS TO SEX.

Year.	Male.	Female.
1918	5	6
1919	52	16
1920	68	43
1921	60	48
1922	34	37
1923	45	37
Total	264	187

From the above table will be seen that approximately 59 per cent are males and 41 per cent females, or a little less than a ratio of 3 to 2. The preponderance of males over females is slightly less than in epidemic meningitis and poliomyelitis. In these diseases about 50 per cent more males than females are attacked.

TABLE III.—AGE DISTRIBUTION.

Age.	1918.	1919.	1920.	1921.	1922.	1923.	Total.
Under 6 mos.	0	3	3	2	2	0	10
6 to 12 "	2	2	2	2	3	1	12
1 to 2 years	0	5	11	11	5	6	38
2 to 5 "	1	10	8	13	8	8	48
5 to 10 "	3	7	21	19	10	9	69
10 to 15 "	1	7	13	5	5	7	38
15 to 20 "	1	7	5	9	6	10	38
20 to 30 "	2	10	22	24	10	12	80
30 to 40 "	0	9	17	9	6	11	52
40 to 50 "	1	7	8	7	5	8	36
50 to 60 "	0	1	0	7	9	6	23
over 60 "	0	0	1	1	1	4	7
							451

It will be seen from Table III that of the 451 cases 234 were more than fifteen years of age and 217 cases were less than fifteen years of age. This is a larger proportion of cases in childhood than is reported by most workers. But we see an unusually large number of cases in children because many physicians in the city are accustomed to call us to help them in the diagnosis of meningeal conditions in children.

For some time we have felt that cases in children were frequently overlooked. If we have made an unusually large percentage of mistakes in the diagnosis of epidemic encephalitis in young children we have made it consistently. Up to the middle of May, 1921, when 274 cases had been studied they were equally divided between patients more than fifteen years of age and those younger.[1] Our findings are corroborated by the work of Happ and Mason,[2] whose age distribution of cases is almost the same as ours.

In contrast to this, about 65 per cent of cases of epidemic meningitis and about 90 per cent of cases of poliomyelitis are less than ten years of age.

Symptomatology. While the chief symptoms are those referable to the central nervous system, there are also symptoms, such as fever, which is usually low and irregular, vomiting and malaise, which may be caused by a general toxemia.

The onset is usually gradual but in a certain percentage of cases it may be abrupt. It is more likely to be sudden in children than in adults. The symptoms referable to the central nervous system are of the greatest possible variety and vary widely in the same patient during the course of the disease, which is often greatly prolonged. This indicates that we are dealing with a virus which may involve any part or combination of parts of the central nervous system and which may progress from one part to another during the illness. This is in marked contrast to the action of the virus in poliomyelitis which attacks suddenly and has usually progressed to the maximum within five to seven days. In poliomyelitis the action of the virus is far more selective, and the greatest damage is done to the cells of the motor area, especially to the cells of the anterior horns of the spinal cord.

We have made no attempt to divide our cases into groups. The multiplicity of symptoms necessitates so large a number of groups that the classification becomes too unwieldy for the use of the general practitioner. Moreover, on account of the progress of the disease the same patient would often fall into any one of several groups, depending on the time at which he was seen.

So much has been written on the symptomatology of epidemic encephalitis that our discussion will be brief. We do wish to emphasize the fact that quite often the symptoms are mild and in other instances different from those originally considered pathognomonic. We feel that the diagnosis is missed in many instances because the physicians are looking for lethargy, asthenia and cranial nerve palsies. While extreme lethargy and somnolence are very characteristic when present, a fairly large group of cases suffer from restlessness and insomnia. In some patients both somnolence and insomnia are present at different stages of the disease.

Ocular disturbances of various kinds are of frequent occurrence. Attacks of diplopia or blurring of vision are sometimes the earliest distinctive symptoms. These attacks may last for only a short time in the early stages or they may occur at intervals for a considerable period. Sometimes the diplopia or blurring is fairly continuous over most of the illness. Loss of vision, usually temporary, is occasionally seen. Other phenomena that are sometimes noted are: Ptosis, either unilateral or bilateral; strabismus, nystagmus and hippus. In one instance there occasionally took place

convulsive twitchings of the eyes which then snapped quickly to the left, and remained fixed for two or three minutes. These seizures occurred at frequent intervals during the height of the disease, but disappeared entirely as the patient recovered. In another case the eyeballs performed in succession a curious, nearly complete rotation, with the pupils looking inward. While one eye was in motion the other eye remained quiet, but there was more or less twitching of the lips and face muscles on the same side. While a large percentage of cases show a normal fundus, a slight haziness of the disc has been seen in a certain number of cases. Various degrees of optic neuritis with or without choking has been observed less often. Sometimes in late cases there is secondary optic atrophy.

In addition to the lethargy or excitability which are very common symptoms, and have already been referred to, delirium is not infrequently present. The delirium may last for a considerable time, or may occur at frequent intervals, lasting only for a few minutes. In other instances the patient is acutely maniacal for varying lengths of time. Catatonia is occasionally seen.

Sensory Disturbances. Headache is an almost constant symptom. Lancinating pains due to involvement of the posterior nerve roots are fairly common. These affect most commonly the arms and legs, but the thoracic muscles are sometimes involved. Numbness or tingling are less frequent symptoms. Occasionally there is loss of sensation, involving one or both legs and lower part of the trunk, resembling a hemitransverse or a transverse myelitis.

Trophic Disturbances. These are rare but do occur during the early or later stages of the disease. Repeated ulcerations of the cornea were seen in one patient beginning during the comparative early stages and lasting for several months. In another case there was an extensive furunculosis late in the disease, and in another case, also late, there were frequent attacks of stomatitis, thought to be trophic in origin. In one case the teeth decayed very badly after the attack of encephalitis and in another there was alopecia.

Motor Symptoms. One of the most striking of the motor symptoms which is found in a certain proportion of the cases is hypertonicity of the muscles. This is shown in the masklike expression of the face, in the general muscular rigidity and the slow movements. The rigidity of the neck due to this general hypertonicity must be sharply differentiated from the rigidity due to inflammation of the meninges. Muscular twitchings are a common phenomenon. They may be of several varieties. Myoclonic contractions may involve a single muscle or any group of muscles. Tetanic spasms are less common. Occasionally a persistent hiccough is seen. Tremors of various types frequently occur. They may be very fine or assume a choreiform or athetoid character. Convulsions are common in children. Paralysis or pareses are very frequent. Involvement of the oculomotor apparatus has already been referred

to. Weakness or paralysis of the muscles of deglutition is comparatively rare. Facial palsies may be either of the central or peripheral type. Practically any form or combination of forms of extremity paralysis or paresis may occur, and this is usually of the spastic type, although not invariably so. The disturbances of speech are a little difficult to group. Some in which there is an obvious dysarthria are probably due to disturbed function of the motor mechanism. In other instances there is a great delay in answering questions. Speech may be hesitant, slow or indistinct.

The reflexes, superficial as well as deep, may be normal, diminished or exaggerated and may be equal or unequal. An Argyll-Robertson pupil is often seen, while loss of accommodation reflex is less common.

The Babinski and confirmatory signs are often present, and the Brudzinski sign is common. The Kernig sign is frequently present. Both patellar and ankle clonus are occasionally obtained.

Other symptoms may be noted, most of these evidences of a systemic infection. Fever is a very constant sign. It is usually low and irregular. Occasionally it is subnormal for a part of the illness. Vomiting is fairly common early in the disease. An obstinate constipation is quite characteristic. Jaundice is sometimes seen but is rare. Bladder disturbances are not infrequent. There may be either incontinence or retention. Hematuria has occurred in two or three instances. Disturbances of the respiratory rhythm occasionally occur. They may take the form of very rapid respiration of forced inspiration. The Biot type is fairly common. Cheyne-Stokes is rare except in the terminal phases. Profuse sweating is a rather characteristic sign and occurs not infrequently. Epistaxis has been noticed as an early sign but has been seen in a very few cases.

It may be well to say a few words about the symptomatology in children, as it is our impression that the diagnosis is often missed. In many cases the symptoms are milder than in adults; in others they are more atypical. Probably the most common form in children is that resembling an early tuberculous meningitis. In these cases the diagnosis can be made only by repeated examination of the spinal fluids. In a certain number of cases the children show symptoms quite unlike those we consider characteristic of epidemic encephalitis. The following is a case in point:

G. L., a girl, aged five and a half years, was seen, February 14, 1921. She had had poliomyelitis in 1916, with paralysis of the right arm and leg. The paralysis of the leg had nearly cleared up. The present illness had begun three weeks before with headache, vomiting, convulsion, delirium and irregular fever reaching 103°. No lumbar puncture had been done. On February 14 she was crying out constantly in a meaningless fashion and was

apparently blind. A lumbar puncture was done, yielding 20 cc. of clear fluid with characteristic findings. The temperature began to subside after the puncture but the screaming persisted for several days and then she began weeping. This lasted for two or three days. Then the condition began to improve. The sight returned, the child began to speak rationally, but was slow in remembering and speaking. The improvement continued until March 13, when after an automobile ride she had a convulsion and became unconscious. Cheyne-Stokes respiration developed, the pulse was feeble and there was cyanosis. Another lumbar puncture was done that afternoon, yielding a clear fluid under increased pressure. This was followed by immediate improvement, and the next day she seemed as well as she had been before the convulsion. The improvement continued, although for several weeks she had a slight rise in temperature every second or third day. Three years later she was reported to be in excellent condition with no after effects.

Differential Diagnosis. The symptomatology of epidemic encephalitis is so varied that a complete differential diagnosis would necessitate a discussion of a very large number of diseases of the central nervous system and many of the acute infections. We shall attempt to discuss the differentiation from only the most important of these.

Tuberculous meningitis is probably the disease from which epidemic encephalitis is most often to be differentiated. The diagnosis may be absolutely made by examination of the spinal fluid and therefore time will not be taken to discuss the different points of clinical diagnosis as they are often misleading. Diplopia, for example, occasionally occurs in tuberculous meningitis. The finding of tubercles in the choroid also makes the diagnosis of tuberculous meningitis certain. The differentiation from the other forms of meningitis is less difficult, but even here mistakes are sometimes made. In purulent meningitis diplopia or disturbances of vision sometimes occurs. A lumbar puncture, of course, immediately makes the diagnosis.

The differentiation from poliomyelitis is usually made, especially from the spinal form. From certain forms that have been described in the past as the encephalitic type of poliomyelitis, the diagnosis at present is a matter of personal opinion. Certain authorities consider that cases previously diagnosed as the encephalitic type of poliomyelitis were really cases of epidemic encephalitis, and it is possible that the classification of poliomyelitis will have to be revised.

The differential diagnosis from brain tumor or abscess of the brain is often made only after extensive radiographic studies or at autopsy. These conditions are so infrequent that the percentage of error in a large series of cases is exceedingly small.

Syphilis of the central nervous system in some cases can only be differentiated by laboratory aid, the Wassermann test.

Cerebral hemorrhage and thrombosis are often mistaken for epidemic encephalitis and *vice versa*. The differential diagnosis is often extremely difficult, especially from cerebral thrombosis. A hemorrhagic fluid makes the diagnosis of cerebral hemorrhage very probable, although blood-tinged fluids may be found in cases of encephalitis.

Cardionephritic conditions, especially in the pre-uremic stages, frequently resemble epidemic encephalitis. Studies of the blood chemistry and determination of renal function will prove the determining factors in establishing final diagnosis in this type of case.

Certain forms of mental disease, dementia precox, for instance often present signs and symptoms similar to those of epidemic encephalitis. The case may have to be followed for some time before a definite diagnosis can be made.

Mention must also be made of encephalitis following acute infections, especially measles. The history of a recent acute infection will be the determining factor in making the diagnosis as the symptomatology and spinal fluid findings may be similar in the two conditions.

Laboratory Aids in Diagnosis. The blood examination is not at all characteristic in epidemic encephalitis. The blood count usually shows a low leukocytosis from 10,000 to 15,000 but sometimes a little higher. The blood cultures are sterile. The analysis of the spinal fluid is the most diagnostic laboratory aid. The spinal fluid is usually clear and increased in amount; sometimes it is slightly hazy and it may at times be yellowish. There have been instances where we obtained a blood-tinged fluid. The cells are usually slightly or moderately increased, the cell count being ordinarily less than a 100, with a preponderance of mononuclears. Occasionally there may be a larger increase in the number of cells up to 1000 or more. A preponderance of polymorphonuclears may at times occur. With but few exceptions we have found a slight or moderate increase in albumin and globulin content. Fehling's solution is promptly and well reduced, denoting a normal or even more than a normal amount of sugar in the spinal fluid. Of late we have used the quantitative method of determining the amount of sugar in the spinal fluid, and we have found the figures to range between 50 mg. and 100 mg. of sugar per 100 cc. Bacteriologically the fluid is sterile. These findings, while characteristic, are by no means pathognomonic, since similar findings are obtained in poliomyelitis, in some instances of syphilis of the central nervous system and early in tuberculous meningitis.

It may not be amiss to discuss in more detail the importance of the sugar content of the spinal fluid. Certain writers have stated

that an increase in the sugar content is pathognomonic of epidemic encephalitis. While it is frequently found in epidemic encephalitis, it is also found occasionally in poliomyelitis, syphilis of the central nervous system and even in meningism. The determination of the spinal fluid sugar is of most value in differentiating tuberculous meningitis. In this disease, when well advanced, the spinal fluid sugar is usually, but not invariably, greatly diminished.

Mention should also be made of the Wassermann test which should always be done when there is any suspicion of syphilis. The colloidal-gold reaction is not so important, since luetic and paretic curves are fairly common findings in epidemic encephalitis.

In differentiating tuberculous meningitis from epidemic encephalitis, if the routine spinal-fluid examination is not definite, recourse must be had to guinea-pig inoculation.

In a few instances where the diagnosis was unquestionably epidemic encephalitis we have found a normal spinal fluid. Other writers have reported a fairly large proportion of normal spinal fluids. However, a study of the spinal fluid analysis in many of our leading hospitals has convinced us that such examinations are often incomplete.

Pathology. Epidemic encephalitis belongs to the class of inflammatory diseases in which also are included poliomyelitis, syphilitic lesions of the central nervous system and trypanosomiasis. While these different diseases have, broadly speaking, certain characteristics, the cases in a given class differ so widely that it is difficult, if not impossible, to accurately diagnose by a study of the pathology alone, the less typical cases.

The meninges are usually described as showing only slight changes—an increase in the cellular content, particularly in the neighborhood of the bloodvessels of the pia-arachnoid. The cerebral cortex is generally normal, except for congestion of the vessel of the leptomeninges. In the brain substance the changes are most marked in the basal nuclei of the brain, the upper part of the pons and peduncles, the gray matter of the floor of the fourth ventricle and the aqueduct of Sylvius. The changes in the medulla and cord are often reported as less pronounced, though observers have noted the same changes occurring in the upper section of the cord. This was certainly observed in one of our cases, an adult, which came to necropsy. (Reported in the *International Clinics*, vol. 2, series 29.)

The lesions are generally described as consisting of four kinds:

1. Infiltration of the walls of the small vessels with lymphocytes and plasma cells.

2. Foci of interstitial and parenchymatous infiltration with round cells. In this reaction neuroglia cells may take part.

3. Lesions of the nerve cells—usually not so extensive as in poliomyelitis and with less neuronophagia. These lesions of the

cells usually occur when the inflammatory process takes place in the gray matter, but they may develop in the absence of an inflammatory reaction. Such is the case with regard to the cells of Purkinje in the cerebellum where inflammatory changes are almost entirely absent.

4. Foci of perivascular hemorrhage. The vessel walls are usually not necrosed.

In connection with the statement that lesions of the cells may occur in regions where there is no evidence of inflammatory reaction, it is interesting to recall that Abramson,[3] in a very excellent study of the pathology of poliomyelitis made at the Research Laboratory during the epidemic of 1916, brought out the same fact in regard to the lesions of poliomyelitis.

Treatment. While many methods of treating epidemic encephalitis have been tried, there has been such a lack of uniformity in results that it is safe to say that at present there is no specific treatment. The majority of observers have agreed that lumbar puncture is beneficial. Some cases seem to do better with repeated lumbar punctures; others are apparently unaffected. None of the cases we have observed have suffered ill effects from lumbar puncture. No definite rule as to the repetition of lumbar puncture can be followed. We have been guided by the clinical condition and the reaction to lumbar puncture, also by pressure symptoms and amount of fluid removed. In some cases the beneficial effects following lumbar puncture have been striking. The following case illustrates this:

N. P., a man, aged twenty-nine years, was seen, January 1, 1923. Past history and family history are unimportant. Present illness developed rather suddenly on December 25, with chills, headache and fever, 103.5°, but without vomiting. On January 1 the patient still had a temperature of 103°, stiffness of the neck, slight ptosis of the lids and double vision. Patellar reflexes were slightly exaggerated. There were signs of bronchitis in both lungs. The patient was quite nervous and very excitable. The headaches and excitability were gradually getting worse while the diplopia was diminishing. Physical examination was otherwise negative. Lumbar puncture was done and 40 cc. of clear spinal fluid under markedly increased pressure was obtained. On examination the spinal fluid showed a large increase in cells; albumin and globulin, ++; sugar was normal. The patient apparently derived so much relief from the puncture that one was done every other day, seven in all. On January 14, twenty days after the onset, the patient was apparently all right except for slight weakness. He made an uneventful recovery without any sequelæ, and is at work and entirely well today. This is apparently an instance where repeated lumbar punctures proved beneficial.

Except for lumbar puncture, the treatment is symptomatic. The symptoms are so varied that the length of this paper will not warrant a full discussion.

The mortality in our series of cases is given in the following Table IV.

TABLE IV.—MORTALITY.

Age.	1918.	1919.	1920.	1921.	1922.	1923.	Total.	Mortality as to age, per cent.
Under 6 months	..	..	1	1	..	..	2	20.0
6 to 12 "	1	..	1	1	1	..	4	33.3
1 to 2 years	..	3	7	4	2	1	17	45.8
2 to 5 "	..	3	3	2	3	4	15	31.2
5 to 10 "	..	3	9	2	5	..	19	27.5
10 to 15 "	..	1	3	..	..	1	5	13.4
15 to 20 "	1	2	3	..	..	1	7	18.4
20 to 30 "	..	2	8	4	5	2	21	26.2
30 to 40 "	..	1	3	3	..	1	8	15.3
40 to 50 "	..	3	3	1	2	1	10	27.0
50 to 60 "	..	1	..	4	6	4	15	68.2
Over 60 "	..	..	1	..	..	3	4	57.1
Total deaths .	2	19	42	22	24	18	127	
Total No. of cases	11	68	111	108	70	83	451	
Mortality . .	Per cent 18.2	Per cent 27.9	Per cent 37.8	Per cent 23.8	Per cent 34.3	Per cent 21.9	Average mortality	28.2

Course of the Disease. When epidemic encephalitis first appeared it was considered a somewhat acute infection of the central nervous system, more or less like poliomyelitis. As time has gone on and cases have been studied further this opinion has been revised. Now we know that in many instances it assumes a very chronic course with periods of remissions and exacerbations. Sometimes relapses with acute symptoms occur after one or more years of apparently good health. It is not certain whether these are due to a lighting up of the old infection or to a new infection. One of our patients died of a second attack after being apparently well for a year. In other instances a year or more after the patient has apparently recovered, a slowly progressive condition, for example, a Parkinsonian syndrome, develops. This is usually considered a sequela, but the opinion has been expressed that this is a secondary attack or a relapse. In other cases these chronic conditions and progressions follow the more acute stages without any marked improvement in the patient's condition. In general, the course of the disease is similar to that of syphilis of the central nervous system. It must not be forgotten, however, that a fairly

large number of cases have remained well over a period of four or five years. The chronicity and variability of this disease is well brought out by the following case:

The patient, H. F., a female child, aged two years, was taken ill suddenly on August 18, 1923, with fever, 102°, and profuse sweating. The child was also gradually becoming progressively drowsy. The family and past history were negative. The physical examination on the fifth day of her illness showed the child to be acutely ill and apathetic. The temperature was 101°; pulse, 90; respiration, 20. There was definite rigidity of the neck. There was double internal strabismus. All the deep reflexes were normal, but the abdominals could barely be elicited. The Kernig, Brudzinski and Babinski signs were all negative. There was a definite weakness of the muscles of the back. A diagnosis of meningitic type of poliomyelitis was made at that time. Lumbar puncture was performed and 30 cc. of clear fluid under increased pressure were obtained. On examination the fluid showed a moderate increase in cells, 98 per cent of which were mononuclears, a slight increase in albumin and globulin and a prompt and good reduction of Fehling's solution. On smear and culture no organisms were found.

October 2, 1923: There was a marked generalized rigidity, particularly of the neck. The strabismus had practically cleared up. The child also presented a typical picture of the Parkinsonian syndrome. There was also Parkinsonian tremor of the hands. It was now obvious that the child was suffering from encephalitis. Lumbar puncture performed at that time yielded 30 cc. of clear fluid under marked increased pressure.

October 17: Child still had Parkinsonian syndrome but to a lesser degree. The tremor was less marked and the child was able to walk a little. The neck was still rigid. Her general appearance was much brighter. On lumbar puncture 45 cc. of clear fluid were obtained.

June 12, 1924: The child was very much improved, but the Parkinsonian appearance was still quite obvious. There was neither rigidity of neck nor tremor of hands.

April 1, 1925: The child showed marked improvement. She was well nourished, bright and cheerful. The Parkinsonian features were disappearing, though her speech was still slow and the facies slightly masked. Her teeth were badly decayed. There was now a new complicating feature—a definite right hemiparesis of the lower motor neuron type as all her deep reflexes on that side were absent. She was unable to walk except when supported and guided. She also had slight inconstant tremor of her right hand.

This case illustrates a number of very interesting points. In

the first place it shows how difficult it is sometimes to make a diagnosis of encephalitis in children. This would have been considered a case of poliomyelitis were it not for the Parkinsonian syndrome that developed two months after the onset of her illness. The chronicity of this disease is also very clearly brought out. The clinical picture has changed a great deal during the different periods of a two-year illness, indicating the involvement of different foci each time. The Parkinsonian syndrome, for instance, was a rather early complication, while later in the course of her illness a right hemiparesis developed as the Parkinsonian picture was clearing up.

We cannot, therefore, consider any of these cases as completely recovered or the sequelæ as permanent until many years have elapsed. It will, indeed, be very interesting and instructive to study the children who had encephalitis a number of years from now.

Sequelæ. It is difficult to obtain a very adequate idea of the sequelæ in epidemic encephalitis. Those who work in neurologic clinics are likely to be unduly impressed with the frequency of sequelæ, since patients with sequelæ go to clinics, while those with complete recovery do not. To obtain a true idea of the frequency of sequelæ it would be necessary to follow a large number of cases for a long time. In the first place, certain patients have symptoms lasting for a year or more, which eventually disappear. For instance, one patient was blind for a year but eventually recovered his sight. Two had change of disposition for about a year and one of them did poorly in school, but both eventually made complete recoveries. In several other instances there were sequelæ lasting several months which eventually disappeared. On the other hand, other patients are in apparently good health for some time, and then develop symptoms which may be considered sequelæ or recrudescences, apparently of a progressive character. Care should, of course, be taken to ascertain that the patient was free from abnormality before the illness. A rather large percentage of our cases had previously suffered from some defect or from some acute infection of the central nervous system before developing epidemic encephalitis. For instance, 2 were definitely mentally defective before the illness; 1 had Little's disease and had developed epilepsy; another had had epilepsy for several years; 1 had had chorea; 3 had had poliomyelitis; 1 had had epidemic meningitis; 1 died from epidemic meningitis while convalescing from epidemic encephalitis.

Of our 451 cases, 127 died. Of the 324 surviving, 36 for one reason or another could not be followed up, leaving 288 cases which were fairly adequately investigated. It was found that 78, or 27 per cent, showed definite sequelæ, while the remainder were carrying on their usual occupations, or in case of children were pro-

gressing in school satisfactorily, and to all intents and purposes showed no evidence of abnormality. Many patients showed several residual defects. Although the number of cases was nearly equally divided between those more than, and those less than, fifteen years of age, it was noted that there were 50 with sequelæ in those more than fifteen years of age and only 28 in the other group. The fact that half of our cases were in children accounts to some extent for our percentage of cases showing sequelæ being less than the percentage of other workers.

The following table shows the distribution of the sequelæ:

TABLE V.

	A. Mental	
I.	Blunting of intelligence	30
II.	Nervousness and irritability	13
III.	Defective memory	5
IV.	Changes in character or in disposition	14
V.	Mania or psychosis	2
	B. Trophic	6
	C. Endocrine	5
	D. Sensory	
I.	Headaches	11
II.	Neuritic pains	6
	E. Motor	
I.	Eye changes	
	(*a*) Pupillary	4
	(*b*) Ptosis	2
	(*c*) Strabismus	2
	(*d*) Nystagmus	1
	(*e*) Diplopia	4
	(*f*) Limitation of motion	4
	(*g*) Blurred vision	4
II.	Paralyses or pareses of muscles of face or extremities	13
III.	Parkinsonian syndrome	11
IV.	Tremors, twitches, spasms	11
V.	Epilepsy	1
VI.	Changes in gait	3
	F. Miscellaneous	
I.	Asthenia	9
II.	Digestive disturbances	4
III.	Disturbances of sleep	10
IV.	Speech disturbance	4
V.	Respiratory disturbances	1
VI.	Sphincteric disturbances	1
VII.	Dizziness	3

A study of the classification shows that the greatest number of sequelæ were mental. The next largest group was of motor origin. It is not within the scope of this paper to classify exactly the various types of mental changes. In some instances they were so slight as to be hardly noticeable. In other instances there was a severe mental deterioration that was apparently progressive. How permanent some of the milder sequelæ will be, it is at present impos-

sible to estimate. We have already mentioned that in several instances sequelæ lasting for a year or more eventually disappeared.

While we have observed only 11 cases of well-developed Parkinsonian syndrome, certain other cases grouped as asthenia presented some of the features suggestive of an early or mild form of this condition. Perhaps the more common of the motor sequelæ is a paralysis or weakness of some group of muscles of the extremities or face. In one case there was a paralysis of the sternocleidomastoid muscle on one side, thus producing a torticollis.

A generalized muscular weakness is a rather common after effect. In some cases it is so severe that it would suggest myasthenia gravis, were it not for the history of the previous attack of encephalitis. In the great majority of cases, however, this general asthenia lasts only for several months or a year. This accounts for the small percentage of asthenia as a sequel in our tabulation.

We have also observed some very interesting but rare sequelæ. Four cases of obesity were noted; 1 case developed diabetes mellitus during her convalescence period. It is possible, of course, that this may have been a mere coincidence. We have not noted the report of this complication in the literature, in contrast to diabetes insipidus which has been observed by several writers. Some interesting trophic disturbances have also been observed, such as alopecia, furunculosis, stomatitis, decay of teeth and corneal ulcers. One patient, an adult, had a very interesting respiratory disturbance. He would get attacks of difficult and labored breathing, lasting from a few seconds to a few minutes. Various types of respiratory difficulties, especially in children, have been referred to in the literature. One patient, a girl, aged seven years, showed two years later some of the symptoms that are considered characteristic of multiple sclerosis—nystagmus, scanning speech and staggering gait. The knee jerks were exaggerated. There was, however, no intention tremor.

It is interesting to compare these frequent, diverse and serious sequelæ of epidemic encephalitis with those of poliomyelitis and epidemic meningitis. In the former the sequelæ are certainly sufficiently grave, but they are confined almost entirely to flaccid paralyses. In meningitis only a very small percentage of sequelæ occurs.

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THE ROLE OF FOCAL INFECTIONS IN THE ETIOLOGY OF ECZEMA.

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Recently dermatologists have shown considerable concern over the comparatively large number of skin diseases of unknown etiology. Chipman[1] in his chairman's address before the section of Dermatology and Syphilology of the American Medical Association at St. Louis, pleaded for more determined effort on the part of dermatologists to discover the etiology of many diseases of the skin. Haase[2] in his chairman's address at San Francisco scored dermatologists for "the lethargy that now seems to possess" them and said that "the remedy for this condition is the thorough recognition that dermatology is nothing more, and certainly nothing less than a highly specialized branch of internal medicine." As an internist, therefore, I am offering no apologies for discussing briefly the etiology of a dermatological condition.

Much has been written of late on the cause of infantile eczema. Most authorities lay stress on sensitization to various foods as being the factor of greatest importance in infants and young children. Since most cases of infantile eczema slowly improve and eventually completely recover without dietary restrictions, it would seem likely, as pointed out by Barber[3] that immunity to food substances is gradually acquired. Exceptions to this rule are found in the case of foods eaten only at rare intervals such as strawberries and lobsters to which some adults continue to be sensitive.

In contrast to the large number of contributions on infantile eczema, very few articles discussing the etiology of eczema in adults have appeared in recent literature. A large number of cases are probably due directly or indirectly to external irritants, and probably another large number are caused by local infectious agents. In the large class due to internal factors, I believe focal infection plays an important role. Sutton[4] briefly calls attention to its importance as an etiological factor in eczema and Chipman[1] mentions focal infection as one of the factors to be considered in every skin lesion of unknown etiology.

The following cases are reported as illustrating the importance of infections of the teeth, tonsils, pharynx and pelvic organs in its etiology, and demonstrate the necessity for thorough examination and consultation in the treatment of this stubborn malady.

Case Reports. Case I.—Miss A., bookkeeper, aged thirty-four years, came to me first on June 29, 1924, complaining of a severe itching eruption on the hands, arms, neck and face. The eruption

had appeared suddenly about six weeks before and had not responded well to treatment by another physician. Some of the lesions would subside for a time and then reappear suddenly, associated with considerable swelling, reminding one of angioneurotic edema. The itching was intense, sleep was disturbed, and the patient had become very nervous. She also complained of headache and pains which radiated up from the neck to the scalp. There had been some socalled dyspepsia, and excessive gas on the stomach and bowels. Careful inquiry revealed no change in diet, habits, environment or clothing which might have caused the eczema.

A complete physical examination showed tenderness over the right iliac fossa and the right hypochondrium. The pulse, temperature, blood pressure, hemoglobin, red cell, white cell and differential counts, urine and stool were normal. Roentgen ray of the teeth disclosed a well defined apical abscess involving the lower left first molar. The fingers were swollen and puffy, and there was some puffiness about the eyes. There were patches of skin on the arms, hands, forearm, neck and face which were covered with dry erythematous lesions. The lesions on the neck had the appearance of lichenification.

I advised immediate eradication of the focus of infection, but the patient wished to delay a few days. Local application of an antipruritic liniment and internal administration of calcium and alkalis gave no relief and on July 2 the offending molar was extracted under procain anesthesia. Exaggeration of the patient's neurotic and fatigue symptoms followed, lasting about ten days. The skin lesions improved at once with no further treatment and were entirely cleared up within a week after the extraction and have not returned. Her gastrointestinal complaints persist, and her general health, though improved, is not robust.

CASE II.—Mrs. M. M., aged fifty-two years, married, housewife, was first seen April 23, 1924, at which time she complained of the severe itching lesions described below. She was first troubled with eczema about five years before at the time of the menopause when it was confined to her ankles. It troubled her more or less until February, 1924, when the lesions became much more widespread. There was no history pointing to possible dietary or external irritant causes for the eczema.

Physical examination was negative except for numerous badly infected teeth and diseased tonsils. The skin eruption was extremely severe and widespread, involving both lower extremities from the knee down, the upper extremities from the elbow down, the upper anterior chest, neck, and face. The lesions were red, inflamed and weeping, and itched intensely. She was extremely nervous, emotionally depressed, and troubled with insomnia. A week of hospital treatment with a modified calamine lotion resulted in considerable

improvement in both general and local manifestations after which she had five teeth extracted under local anesthesia. A severe exacerbation of the eczema followed at once, which failed to respond to the same medication which had given so much relief, but gradually subsided, apparently irrespective of treatment. About two weeks later, she had several more teeth extracted, followed by another severe exacerbation, which in turn gradually subsided, since which time she has been free from symptoms except for an occasional mild eruption about the ankles. She still has a few teeth which are fairly normal. Her tonsils, which are diseased, have not been removed, and it is likely that they are responsible for the persistence of what little eczema remains.

CASE III.—Mrs. S., aged thirty years, housewife, came to me January 14, 1925, complaining of a severe itching eczematoid lesion on the anterior aspect of the neck and chin. The skin was dull red, with fine scales and excoriations. It had appeared suddenly two weeks before and there had been several acute exacerbations when there were small vesicles and considerable subcutaneous infiltration accompanied by a choking sensation and stinging pain in the neck. Her family and personal history were unimportant and the physical examination was negative except for several infected teeth. There had been no changes in diet, and she had taken no medicine which could cause the skin lesions. Possible external irritants were also ruled out. An antipruritic liniment for local application and a mixture of alkalin salts for internal use were prescribed. Improvement commenced immediately following the extraction of four teeth with apical abscesses and continued rapidly for a week, and then more slowly. Within three weeks after the extraction of the teeth she was entirely well and has remained so ever since.

CASE IV.—A physician, aged thirty-four years, who gave a history of repeated attacks of eczema prior to tonsillectomy, ten years previous, developed on February 15, 1925, a severe, acute pharyngitis accompanied by general malaise and fever. The second day scattered itching papular lesions developed on the legs, abdomen and buttocks. At the same time typical patches of dry, itching eczema measuring 5 x 7 cm. appeared on the anterior surface of the lower part of both forearms. There was nothing in the diet, medication or environment which could have caused the skin eruption. The febrile attack lasted two days, but a rather severe pharyngitis persisted about two weeks. The scattered skin lesions persisted only a few days, but the patches of eczema continued for about two weeks and gradually disappeared, without treatment, with the subsidence of the pharyngitis.

CASE V.—Mrs. G., housewife, aged thirty years, first consulted me July 25, 1924, complaining of a very severe generalized itching

eruption having all the classical characteristics of acute eczema. The lesions were almost universal, no part of the body being entirely free. They were flaming red in color and for the most part dry, though some areas presented a weeping surface. Itching was intense, interfering with sleep and producing marked nervousness. The birth of her fourth child had occurred two weeks previously. The labor was a normal one, and the puerperium was uneventful until the fifth day, when she complained of intense soreness in the lower abdomen. The following day she had a considerable elevation of temperature, and the skin lesions above described appeared. During the next week she said she had fever most of the time, but as the fever subsided her eruption also improved. When I first saw her, the pelvic infection had again become active, and her skin lesions were as bad as ever. Pelvic examination revealed an involuting uterus with bilateral acute salpingitis. Physical examination was otherwise negative. Prolonged complete rest in bed with symptomatic treatment resulted in complete subsidence of the pelvic infection. The skin lesions improved without local treatment, concurrently with the improvement of the pelvic condition, and the patient was discharged from treatment at the end of the fourth week of her puerperium. There has been no recurrence of either the pelvic infection or the eczema. Careful search was made for other possible causes of the skin eruption, but none were found.

Comment. A causal relationship between the focal infection and the eczema seems certain in the foregoing cases. The series might be increased by the addition of several cases where the causal relationship is somewhat less clearly defined. Speculation as to the mechanism of this relationship may be of interest. It is possible that the host has become sensitive to the bacterial end-products existing in the focus of infection. The almost explosive suddenness of the onset in 3 of these cases certainly suggests an allergic reaction. The fact that many men believe that infantile eczema is due to protein sensitization would add weight to this theory.

Summary. 1. Five cases of eczema apparently caused by focal infection are reported. In the first 3 cases, recovery followed the removal of abscessed teeth. In the fourth patient, the eczema ran its course concurrently with an acute pharyngitis. In the last case, rapid subsidence of the eruption accompanied improvement of infected pelvic viscera.

2. Careful search was made in each case for other possible causes of the skin lesions, but none were found.

3. Local antipruritic treatment in 4 cases had no effect upon the skin lesions, aside from decreasing the scratching, and improvement seemed to occur in spite of, rather than because of it.

4. The opinion is ventured that focal infection is an important cause of eczema in adults.

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A STUDY OF THE EFFECT PRODUCED ON THE ENZYME CONCENTRATION OF THE DUODENUM BY THE ORAL ADMINISTRATION OF CERTAIN COMMERCIAL PANCREATIC PREPARATIONS.*

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and

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If one may judge by the number of pancreatic preparations placed on the market by reputable firms of pharmaceutical manufacturers there must exist a demand on the part of clinicians for pancreatic extracts which contain in active form the enzymes secreted by this organ, and which if administered in cases where a deficiency of the duodenal enzymes had been demonstrated, would presumably act as an aid to an impaired digestive function. Our knowledge of the action of many drugs on the gastrointestinal tract is still based largely on theory,[1] rather than on experimental findings, and the same criticism may justifiably be applied to our use of glandular preparations.

To test the activity of any pancreatic preparation *in vitro* is an exceedingly simple proposition, but such tests do not necessarily indicate the effectiveness of the same substance when administered by mouth, as in the latter case a number of conditions, not met with in the laboratory digestion experiment must be reckoned with.

In a study of the effectiveness of some commercial pancreas preparations we have therefore attempted to determine the utility of these extracts by a study of the enzymatic activity of the duodenal contents before and after the oral administration of some of these preparations.

Our method of procedure was as follows:

With the subject fasting about fifteen hours the duodenal tube

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was passed and allowed to reach the second portion of the duodenum, the position of the tube being in every case determined by the fluoroscope.

One or two portions of about 10 cc. of duodenal contents were removed and examined for enzymatic activity to serve as controls; the pancreatic preparation to be tested was then given by mouth in the amount stated in Table II, together with 50 cc. of tap water, and samples of duodenal contents were then removed at intervals for analyses.

The duodenal content obtained as above described was assayed for enzymatic activity by the methods of McClure, Wetmore and Reynolds.[2] The several slight modifications to the original methods described in a previous publication[3] were also used in this work. Hydrogen-ion concentrations were determined colorimetrically by means of the Clark-Lubs series of indicators, and a set of buffers that had been checked by the electrometric method.

In Table I are presented the results obtained on four commercial pancreatic preparations when tested *in vitro* for digestive activity.

These tests were carried out as follows: 0.1 per cent solutions of these preparations dissolved in McClure's phosphate mixtures were prepared except in the case of the peptic liquid. This compound is supplied in fluid form, and we, therefore, evaporated 10 cc. to constant weight in an air bath at 110° C., and from the figures for total solids so obtained calculated the dilution of the original preparation required to make a solution containing 0.1 per cent solids. One cubic centimeter portion of the dilutions described above were added to 9 cc. of the substrate used in the McClure method, and the remainder of the test carried on by exactly the same technic as was used for the testing of the enzymatic activity of duodenal contents.

TABLE I.—RESULTS OF IN VITRO TESTS OF PANCREATIC PREPARATIONS.

Preparations.	Per 1 cc. of 0.1 per cent solution of preparation.		
	Amylase Mmg. glucose.	Lipase M10.1N NaOH	Protease Mmg. N2
Number one	5.6	0.7	5.7
Number two	0.73	0.7	4.6
Number three	0	1.2	4.67
Number four	2.38	0.8	0.316

As will be seen by an inspection of the results collected in Table I, all the preparations with which we worked gave evidence when tested *in vitro* of decided digestive power. The figures given in the table are calculated according to the method used by McClure

and his collaborators and should, we feel, not be considered in the light of absolute values but rather as of comparative importance only. Had some other procedure been adopted there is no doubt that the absolute figures given would have been different, although the comparative relations between the various preparations would probably have remained the same.

TABLE II.—RESULTS OBTAINED ON THE ORAL ADMINISTRATION OF PANCREATIC PREPARATIONS AND OF FRESH BEEF PANCREAS.

Pancreatic preparation.	Date.	pH.	Lipase M10.1N NaOH.	Protease Mmg. N.	Amylase Mmg. glucose.	Subject.	Remarks.
Raw beef . .	1/26/25	7.6	0.3	2.4	4.0	1. Normal subject	Fasting sample.
Pancreas . . .	....	7.4	0	2.8	4.6	....	15 minutes after administration.
30 gm. . . .	....	6.2	0.2	5.6	1.2	....	45 minutes after administration.
Preparation No. 2	1/20/24	7.0	3.0	5.5	2.1	2. Normal subject	Fasting sample.
		4.0	0.1	1.6	0.81	....	40 minutes after administration.
gr. vii . . .	....	7.4	2.8	5.7	1.6	....	60 minutes after administration.
Preparation No. 2	1/23/24	7.4	0	1.7	0.7	3. Chronic biliary infection	Fasting sample.
		7.2	0	2.7	0.9		30 minutes after administration.
gr. vii . . .	....	7.2	0	1.7	0.7		60 minutes after administration.
Preparation No. 1	2/16/24	7.2	0.10	1.8	0.55	5. Normal Subject	Fasting sample.
		7.0	1.0	1.8	2.60		30 minutes after administration.
		7.2	1.1	2.5	0.65	....	60 minutes after administration.
gr. vii . . .	....	7.5	1.3	3.1	0.65	....	90 minutes after administration.
Preparation No. 1	3/23/24	7.4	0.3	1.4	1.5	6. Normal Subject	Fasting sample.
		3.4	0.3	0.24	0		30 minutes after administration.
gr. vii . . .	....	3.4	0.1	0.21	0	....	60 minutes after administration.
Preparation No. 3	6/23/24	7.0	0	1.0	0	3. Chronic biliary infection	Fasting sample.
		7.2	1.4	3.4	0.7		30 minutes after administration.
gr. vii . . .	....	7.4	1.8	5.6	0.8		60 minutes after administration.
		5.5	0	2.0	0	....	90 minutes after administration.
Preparation No. 3	1/28/24	7.4	1.5	2.6	0.93	4. Chronic biliary infection	Fasting sample.
		7.4	0.3	2.1	0.8		30 minutes after administration.
gr. vii . . .	....	6.4	1.4	4.0	1.1		60 minutes after administration.
Preparation No. 4	3/23/24	7.6	1.2	1.2	2.1	7. Normal subject	Fasting sample.
		7.8	1.0	1.4	1.2		30 minutes after administration.
15 cc. . . .	....	7.8	1.0	1.7	0.9	....	60 minutes after administration.
Preparation No. 4	3/30/24	7.2	0.2	1.5	1.0	8. Normal subject	Fasting sample.
15 cc. . . .	....	7.3	0.2	2.0	0.93		45 minutes after administration.

Lipase—cc. of 1/10 N. fatty acids formed from oil by 1/50 cc. duodenal contents.
Protease—mg. of non-protein nitrogenous bodies formed from casein by 1/50 cc. duodenal contents.
Amylase—mg. of glucose formed from starch by 1/50 cc. duodenal contents.

In Table II we have collected the results obtained in experiment with fresh pancreas and with four commercial enzyme preparation made on eight subjects.

As a control on the commercial preparations we used for our first experiment fresh raw beef pancreas which had been finely minced after removal of the connective tissue. The subject of this experiment was a medical student who showed no repugnancy over the unusual dose. As will be seen there was a rise of almost 100 per cent in the proteolytic activity, no increase in a lipase and but little in amylase.*

The results on the commercial preparations showed in every case more striking effects produced on the proteolytic activity than on the starch and fat-splitting forms, although in certain experiments an undoubted increase in amylase was observed.

Summary. In a series of observations made on the digestive power of raw beef pancreas and of four commercial pancreatic preparations our results were as follows:

When tested *in vitro* all preparations showed digestive activity as regards proteolytic and lipolytic actions, but one seemed lacking in ability to split cooked starch under these experimental conditions.

In vivo the most striking effect noted was a marked increase in proteolytic activity, although in certain preparations a moderate increase in the ability of the duodenal secretion to split starch and emulsified fat was noted.

In interpreting the difference in the results obtained in the *in vitro* experiments as contrasted with those obtained on the administration of the preparations by mouth one must consider the possibility of stimulation of pancreatic secretion by these preparations as distinguished from the simple increase in the enzymatic concentration of the duodenal contents produced by the enzymes contained in the amount of gland substance taken.

The results presented above may, we believe, be interpreted as furnishing experimental proof of the fact that pancreatic preparations taken by mouth increases the digestive power of the duodenal contents.

* In this connection it seems desirable to call attention to our experiments on the effect of protein administration on the concentration of pancreatic enzymes in the duodenal contents.[4] It was found that the ingestion of protein in the form of lightly boiled egg white, produced an enormous increase in the proteolytic activity of duodenal contents.

In considering the results produced by fresh pancreas and by the dried gland preparation, it would therefore seem justifiable to consider the possibility of stimulation by protein alone.

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SIMPLE LACTATING ADENOMA OF THE BREAST.

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Simple lactating adenoma of the breast is a rare type of tumor; in the past ten years there have been but 2 cases from the surgical services of the University Hospital. The uncommon finding of this tumor in our Clinic, and the failure of some men when reporting large series of breast tumors to mention this type, have prompted an investigation and the reporting of this case.

Case Report. *History.* The patient, a primipara, was admitted to the University Hospital on the service of Dr. Eliason, to whom I am indebted for the privilege of reporting the case. The chief complaint on admission was the presence of a mass in the right breast. The patient, a negress, aged twenty-four years, first noticed a small lump in the breast nine years before. This she described as having been about the size of a small marble. The lump apparently remained stationary in size until the onset of pregnancy. This was one year before admission. At this time she noticed a gradual increase in the size of the mass, which progressed until at the time of delivery, it had attained the size of a chicken's egg. Associated with this enlargement there was some tenderness. After delivery, and with the onset of lactation, it grew rapidly. At time of admission to the hospital, three months after delivery, it was the size of a large orange. Since the time when the tumor was first noticed it has always become hard and slightly painful at the time of menstruation.

Physical Examination. The patient was a well-developed adult negress, aged twenty-four years. She did not appear acutely ill. There was nothing abnormal found on physical examination, except the mass in the right breast. The tumor was rounded, about the size of an orange, and was situated in the upper inner right quadrant. It was discrete, movable noninfiltrative and was not adherent to the skin or underlying tissues. There was no dimpling of the overlying skin or retraction of the nipple. The nodes in the axilla and supraspinous fossæ were not palpable. The Wassermann tests of the blood of the patient and her child were strongly positive.

Operation. A modified Thomas incision was made at the inner angle of the breast. The tumor, which was well encapsulated, was easily separated from the adjacent tissues and removed. The cavity was obliterated by continuous catgut suture. The wound

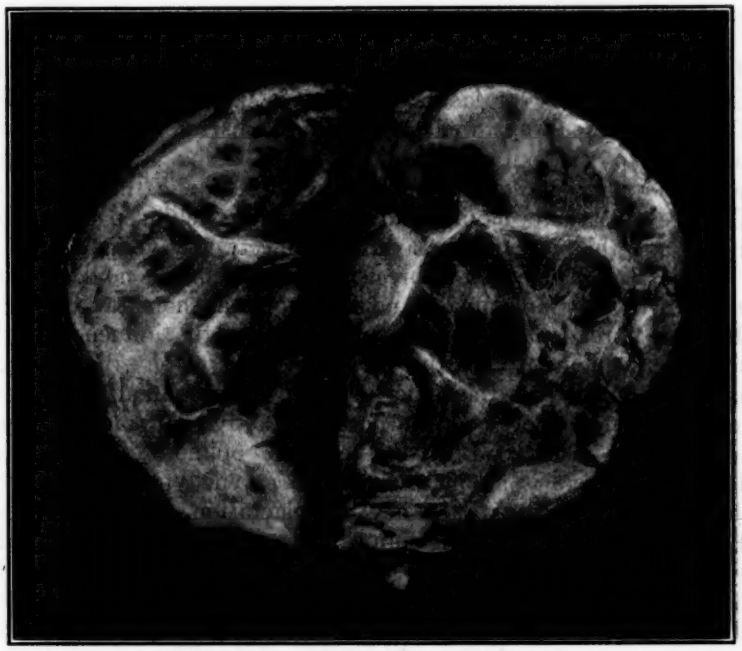
was then closed in layers, leaving a rubber tissue drain in the inner lower angle. The skin was closed with a continuous silk suture.

Examination of the Tumor. The tumor which was removed is shown in the illustration. It was tense, well encapsulated, reddish yellow in color, soft in consistency, lobulated and well circumscribed. On section the cut surface oozed thick cream-colored secretion. When this was scraped off the surface was red to pink in color, somewhat spongy, granular and opaque in appearance, and the lobules were well separated from one another by fibrous bands. There was no macroscopic evidence of cyst formation. The tissue appeared to be saturated with this creamy secretion, which in all probability represented a condensation product of the whole milk of which the water content had been largely reabsorbed.

Microscopic studies showed a fairly uniform structure. The tumor was covered with a well-defined fibrous capsule which gave origin to septa which divided the tumor into well-defined lobules. The acini which constituted the predominant structure showed slight variation in size. They were more or less irregularly circular in outline, and rested upon a very fine stroma of connective tissue. The latter was scant, so much so, in fact, that the basement membranes of the acini appeared to be in direct apposition. The epithelial cells ranged from a large low columnar type to a large cuboidal type and were for the greater part in single layers, resting upon the basement membrane. A slight proliferation of the cells into the acinar cavities was noted in some places. The nuclei of the cells were disproportionately small, when compared with the size of the cell, and stained deeply. The cytoplasm, which was quite abundant, was granular and showed vacuoles. The membrane of many of the cells was very indefinitely outlined, and appeared to be undergoing degeneration. The cavities of the distended acini contained a granular secretion, fat droplets and cellular débris.

Cases Reported in Literature. Simple adenomata of the breast are exceedingly rare tumors. One of the first cases was reported by Billroth in a married, nulliparous woman, aged twenty-four years. The location, size and general description of the tumor corresponds very closely to ours, but the tumor described by Billroth showed no evidence of lactation. Powers described a simple adenoma which had been removed from the breast of a woman four months pregnant. Grossly and microscopically this tumor was very similar to our own, except for the absence of lactation. Gross reports one removed from the breast of a girl, aged sixteen years, which was first noticed by the patient three months before. It was oval in shape, quite nodular and measured $1\frac{3}{4}$ by $1\frac{1}{4}$ by $\frac{1}{4}$ inches. There was no mention of lactation. Speese reports a tumor removed from the breast of a primipara, aged twenty-one years. The growth was present in the breast for several years,

but produced no symptoms. Following childbirth and coincident with the onset of lactation, the tumor, which had been the size of a walnut, began to enlarge rapidly. On examination it was found to be a simple lactating adenoma. Deaver and McFarland add one to the list. This tumor was removed by Dr. John B. Deaver from a patient in the Lankenau Hospital. The size, location and microscopic and macroscopic pictures were almost identical with the tumor reported herewith.



Lactating adenoma of the breast.

Classification. The term adenoma is often used inaccurately in describing benign growths of the breast. The majority of the benign breast tumors contain adnomatous tissue but in varying quantities. This fact is the basis for the classification of the adenomata. The greater number are grouped under the term fibroadenoma from the fact that fibrous tissue is the chief constituent of the tumor. Adenofibromata are less common than the former but by no means rare. In these the glandular tissue is a little in excess of the fibrosis tissue. The simple adenomata are, as already mentioned, very rare, being by far the rarest type of benign tumor found in the breast. The prevailing tissue is glandular in type with very little fibrous stroma.

Discussion. Uncomplicated benign tumors of the breast give rise to a few symptoms. There may or may not be very slight

pain at the time of menstruation. During pregnancy and lactation, however, they usually show great change. The glandular constituents of the tumor are apparently stimulated by the hormone which acts upon the normal gland tissue, with lactation hypertrophy as the result. Severe pains are experienced, especially during lactation, incident to the sudden enlargement of the tumor. This is probably due to the fact that there is no duct communication with the mammary gland proper. The result is that the secretion is stored up in the tissues and the tumor becomes very tense and painful.

The tumor is found to range in size from that of a walnut to that of an orange. It grows very slowly, if at all, except at the time of pregnancy or lactation, when it increases quite rapidly. The growth is always well encapsulated, discrete, movable, nonadherent to the skin and noninfiltrative. The adjacent lymph nodes do not enlarge in the absence of complicating infection. The age of patients having had these tumors removed is between fifteen and thirty years, the average being twenty years.

McFarland in referring to breast adenomata makes no distinction between the fibroadenomata and the simple adenomata. He feels that the fibroadenomata when placed under the influence of the hormones which activate the breast to hypertrophy during pregnancy are affected in the same way. It is his opinion that simple adenomata are the result of hormone activity upon the fibroadenomata. Bloodgood is of the same opinion. There is no doubt that there is an increase in the parenchymatous tissue in these tumors during pregnancy and lactation, but it is rather difficult to believe that all simple adenomata are physiologically active fibroadenomata. The fact that the cases reported by Billroth and Gross gave no history of pregnancy or of having borne children makes one wonder if the tumor in these patients at least was not a simple adenoma from the start. There is, however, always a possibility of inaccuracy in historical data and the few cases of simple adenomata reported as occurring independent of pregnancy and lactation are not sufficient evidence to refute the opinion of the men quoted above, namely, that simple adenomata are fibroadenomata altered in structure through physiologic activity.

The differential diagnosis between simple adenomata, fibroadenomata and adenofibromata is impossible except by microscopic study.

This, however, is of little practical moment since the treatment for all three types is excision. The possibility of these tumors undergoing malignant change has given rise to much discussion, especially in the case of the simple adenoma which would seem from its structure to be most likely to do so. Any tumor which consists of a disproportionate number of epithelial cells should always be considered as having great malignant potentialities.

Bloodgood makes no mention of these tumors becoming malignant, but he advises their removal lest this change occur.

Conclusions. 1. The average age of the patients having had these tumors is between the fifteenth and thirtieth years.

2. Adenomata give rise to very few symptoms except during menstruation, pregnancy and lactation, when they increase quite rapidly in size.

3. The simple adenomata are the least common of all the types found.

4. The treatment of these tumors is excision.

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THE PHARMACOLOGIC AND THERAPEUTIC PROPERTIES OF THE SULPHOCYANATES.*

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Personal experience for a number of years has convinced me that sodium sulphocyanate is one of the most efficacious remedies available for the treatment of arterial hypertension. There exists, however, a remarkable paucity of readily available information concerning the drug, especially in the English language; the treatment of the subject in the current manuals on pharmacology is incomplete, inadequate and questionable. It is with the purpose of obtaining, collecting and presenting information relating to the pharmacologic and therapeutic properties of the sulphocyantes, and directing attention to a valuable remedial agent, that this study is presented.

There is a profusion of synonyms used to designate sulphocyanic acid and its compounds. The acid in English is interchangeably termed sulphocyanic and thiocyanic acid; in German it is usually called rhodanic acid (Rhodansäure), also Rhodanwasserstoffsäure, Schwefelcyansäure, Schwefelcyanwasserstoffsäure, Sulfocyanwasserstoffsäure, etc. Its salts are in English variously called sulpho-

* Read before the American Congress on Internal Medicine, Washington, D. C., March 10, 1925.

cyanates, sulphocyanids, thiocyanates and thiocyanids; in German, rhodanates, rhodanids, or very commonly rhodan compounds. All these synonyms must be borne in mind in consulting the index to the literature.

Sulphocyanic acid, HCNS, is an uncertain and unstable substance, easily decomposed by boiling and by exposure to air. Its compounds are very stable and definite. It forms a large number of salts, and has chemical relationships with various complex organic compounds, especially the purin group. Its alkaline salts, the sulphocyanates of sodium, potassium and ammonium have been most studied from a physiologic and pharmacologic standpoint, and are the compounds especially considered in this paper. These are white crystalline substances, saline in taste and very soluble in water and alcohol.

Sulphocyanate solutions are turned to a brilliant dark red color by the addition of a drop or two of ferric chlorid solution, decolorizing again on the further addition of an excess of mercuric chlorid; but these color changes do not take place if the reaction of the mixture is markedly alkaline. This forms a very sensitive test for the presence of sulphocyanate; the reaction is well marked in solutions of 1 to 10,000, and weakly shown in a dilution of 1 to 100,000. I have made quantitative determinations in saliva by comparing in a colorimeter 5 cc. of the clear colorless filtered saliva to which 1 drop of the official solution of ferric chlorid was added, with a 1 to 5000 solution of sodium sulphocyanate similarly treated. Normal saliva yields the sulphocyanate reaction; the urine of persons taking this drug on the addition of 1 or 2 drops of ferric chlorid solution turns a characteristic brown to dark red color, slightly different from the cherry color yielded with diacetic acid, and markedly different from the purple-black color formed with salicylic acid. The faint brownish color frequently obtained in the routine testing of urines for diacetic acid with ferric chlorid is perhaps due to the presence of a trace of sulphocyanate.

As has been long known, sulphocyanate (of sodium or potassium) occurs normally in the saliva; considerable study has been given to this point. It also occurs in other secretions and body fluids, as the tears and gastric juice. The mode of its formation has not been completely worked out; but it is generally supposed to result from the katabolism of sulphur-containing proteins, and to be formed mainly in the salivary glands, from which it is secreted into the saliva and then swallowed and absorbed into the system. The ordinary sulphocyanate content of the saliva approaches about 0.01 per cent, or 1 in 10,000. If the secretion of saliva amounts, as estimated, to a liter or more in twenty-four hours the amount of sulphocyanate swallowed from this source would approach 0.1 gm. daily. The sulphocyanate content of the saliva varies under different conditions; it is, for instance, diminished or disappears

entirely during the administration of iodin and increased by the use of tobacco.

I have found sodium sulphocyanate anticoagulant when added to blood to the extent of 2 per cent. One part of saliva added to 4 parts of blood similarly prevents coagulation. I have also found sodium sulphocyanate isotonic with blood in concentration of 1.5 to 2 per cent.

Weak solutions of the alkaline sulphocyanates possess no bactericidal properties. Some of the more complex organic compounds of sulphocyanic acid are apparently much more bactericidal.

Pharmacology. The earliest studies of the pharmacologic properties of the sulphocyanates were presented in 1857 by Claude Bernard, whose observations, however, were very incomplete. Subsequent important studies were presented by a number of investigators, notably by Setschenow in 1858, Ollivier and Bergeron in 1863, Dubreuil and Legros in 1867, Laborde in 1880, Paschkis in 1885, Martinotti in 1896, Edinger and Treupel in 1900–1901, Lodholz in 1905 and others.

Personal Observations. I have made some personal studies of the effects of administration of sodium sulphocyanate to guinea pigs. It was given both by mouth and by intraperitoneal injection. By the oral avenue there was some uncertainty as to the exact amounts swallowed, so that the intraperitoneal dosage was more definite and accurate.

In sufficient doses sodium sulphocyanate was found to be highly toxic for the guinea pigs, death occurring in from a few hours to several days, the time varying with the amount and concentration of the drug employed.

Doses of 100 mg. per kilogram of body weight produced no evident symptoms. The minimum lethal dose observed was 200 mg. per kilogram of weight. Some animals, however, survived doses as high as 300 mg. per kilogram. Dilute solutions (2 per cent) were less toxic or more slowly toxic than concentrated solutions (10 per cent).

Immediately after swallowing a concentrated solution of sodium sulphocyanate the animals would frequently for a few minutes sneeze, or hiccough, or cough; while immediately following an intraperitoneal injection there might be some momentary shock. Aside from these the effects were the same after both methods of administration. After a few hours (the period varying with the size of the dose), during which the animal would appear normal or perhaps somewhat sluggish, protracted diarrhea usually appeared in the toxic cases, frequently with edema, congestion and hemorrhage at the anus. With this, progressive and extreme loss of weight occurred, to as much as one-third of the original weight; loss of weight of 25 per cent was observed in one instance with ultimate recovery. Later there appeared evidences of spinal irri-

tation. The animals became rigid, at first showing a notable spasticity of the rear extremities, which would be stiffly extended and abducted, so as to impede locomotion. When turned on its side the animal would find it difficult or impossible to resume the upright position. It would lie stiffly sprawled out on its belly or on its side. Later the rigidity would increase and involve the entire body, general convulsive twitchings and movements would occur and the animal would die in coma. With large doses death would occur in four or five hours; with smaller lethal doses the course of the case would usually be within two or three days, the maximum observed being six days. In 1 nonfatal case the only result was abortion; in 1 fatal case abortion failed to occur in a pregnant animal. Necropsies showed little abnormal.

Similar results were obtained with potassium and ammonium sulphocyanates.

The results of the available pharmacologic investigations of the sulphocyanates may be summarized as follows:

Ingested sulphocyanates are excreted as such by the kidneys, and are markedly demonstrable in the urine of persons taking the drug. Their excretion takes place very slowly; after discontinuing the ingestion of the drug the urine does not become free of sulphocyanate until after a number of days. This suggests the possibility of an accumulation of the drug in the system. Ingested sulphocyanate is also secreted into the saliva, like the iodids; the sulphocyanate content of the saliva increases while taking the drug, and after discontinuance of the latter the increase in the saliva persists for some time after it has disappeared from the urine. Sulphocyanates, therefore, pass through the organism unchanged; Pollak was able to obtain from the urine the same amounts as were ingested. They do not undergo transformation into the much more deadly hydrocyanic acid and cyanids. Both *in vitro* and *in vivo* the reverse change is readily effected, that is, from hydrocyanic to sulphocyanic acid. Sodium cyanid intravenously injected has been found to be rapidly converted into sodium sulphocyanate; and in case of poisoning with hydrocyanic acid or cyanids the intravenous injection of sodium sulphid and hyposulphite has been advised, with the object of converting them into the less toxic sodium sulphocyanate. The sulphocyanates form a well-marked group of compounds distinct from the prussic acid and cyanid group, and there need be no apprehension of the formation of the latter from the former in therapeutic use.

According to Edinger and Treupel, ingested sodium sulphocyanate increases the urinary output of sulphur and nitrogen and lessens urinary acidity.

Prolonged administration of sulphocyanates to animals in considerable (sublethal) amounts produces no perceptible harmful

effects. In human subjects, however, the continued use of sulphocyanate in therapeutic amounts is capable of producing disagreeable symptoms.

In large doses sulphocyanate is a powerful poison and exerts very potent and marked pharmacologic effects. The action varies somewhat in different animals, but in general is as follows:

To a certain extent, as stressed by Bernard and the earlier investigators, it is a direct muscle poison, abolishing muscular activity.

Intravenously injected into dogs in sufficiently large doses (100 mg. per kilogram of body weight) it causes immediate and permanent cessation of the heart action, usually with a convulsion at the moment of cardiac arrest (Lodholz). This may be due to direct action on the heart muscle, as well as to stimulation of inhibition. In doses not immediately fatal its immediate effect is to cause a marked and protracted increase of blood pressure (even to double the original height) and to increase the rate and amplitude of the respiratory movements (Paschkis). Cardiac arrhythmia may, or may not, be produced; the cardiac inhibitory mechanism is believed to be stimulated.

In from one to several hours after the introduction of sufficient doses of sulphocyanate, by mouth or otherwise, marked diarrhea sets in, supposedly caused by stimulation of peristalsis, similar to that produced by nicotin. With the diarrhea occurs much loss of weight.

Diuretic action has been noted only in rabbits.

The final stage of sulphocyanate poisoning consists of intense stimulation and irritation of the motor cells of the spinal cord, of quite the same order of intensity as that produced by strychnine or tetanus. The animal shows weakness, unsteadiness, tremors, inability to regain the upright position after being placed on its side or back, and perhaps a preliminary paralytic phase; the posterior extremities are particularly involved. These conditions deepen into general tonic and clonic convulsions, general quivering, rigidity, coma, death.

It has been a moot question whether the pharmacologic activities of the sulphocyanates are produced by the sulphocyanic radicle, the bases or by "salt action." The effects produced are so distinctive, however, so different in like amounts from the properties of other salts of the same bases that to me they seem clearly to be due to the sulphocyanic radicle. Some salt action is, however, evidenced by a somewhat greater toxicity of the more concentrated solutions. The sulphocyanate of potassium has been generally regarded as more toxic than that of sodium; but I do not know of any comparative studies demonstrating this.

The period covered by the course of a lethal case of sulphocyanate poisoning ranges from immediate death to several days, varying with the size of the dose and method of administration.

The minimum doses of sodium sulphocyanate found lethal by various observers vary with different animals, but are usually stated to range around 500 mg. per kilogram of body weight. In my own experiments the minimum doses which I found fatal to guinea pigs were somewhat lower, from 200 to 400 mg. per kilogram, some dying from 200, others surviving 300 mg. In the same ratio the minimum lethal dose of sodium sulphocyanate for a medium-sized man (weighing 70 kg., or 154 pounds) would be from 15 to 30 gm. ($\frac{1}{2}$ to 1 ounce).

Toxicology. I have found 4 cases in the literature bearing on the toxicity of sulphocyanates in man, as follows:

The first case (reported by Lesser, 1898) was that of a magician, aged fifty-eight years, tabetic, who in his tricks used potassium sulphocyanate to convert iron-containing water into "red wine." Being in destitute circumstances, he with suicidal intent consumed a quantity of the salt (amount not stated) dissolved in beer. He died in about ten hours. Necropsy showed corrosions and hemorrhages of the gastric mucosa, and traces of potassium sulphocyanate were demonstrated in many of the fluids and organs of the body.

The second case was that of a woman, who, after taking 0.3 gm. of ammonium sulphocyanate, developed convulsions, and died in twenty-eight hours. The case is briefly reported in a manual of toxicology by Kobert, 1906. The original report was not found; the details given are very meager, and the case is doubtful, since abundant clinical and experimental experience would indicate that the quantity stated, 0.3 gm., would be entirely insufficient to produce any material effects. Perhaps the statement of the amount was erroneous.

The third case (Adler, 1911) was that of an engineer, aged twenty-four years, who took 30 gm. of pure ammonium sulphocyanate dissolved in 200 cc. of water at midnight. A quarter of an hour later he vomited once, and then retired and slept until morning. About 7 A.M. he was awakened by an alarm clock, and on arising vomited once more and experienced a little vertigo. A physician then administered copper sulphate as an emetic, which was followed by further vomiting. After this there was moderate epigastric pain and a transient disagreeable sensation in the region of the bladder. There were no other symptoms, except that on the following day there may have been some chromatopsia, the skin of himself and other persons (but not white objects) seeming to have a yellowish tinge. The temperature on the first day was 37.1° C.; on the second day, 37.3° C.; third day, 37.4° C. (99.3° F.); after that not over 37° C. The systolic blood pressure was 95 to 100. The blood, urine, heart, pulse and so forth were normal. The urine showed a sulphocyanate reaction for twelve days.

The fourth case (Vintilesco and Popesco, 1916) was that of a

magistrate, aged twenty-seven years, living in a hotel, who showed signs of mental aberration and poisoning and was sent to a hospital. On admission there he showed extreme cerebral agitation, with delirium and occasional convulsions. He became progressively worse, with anuria, cold sweats, total loss of consciousness, rigidity of the extensor muscles of the head and spinal column. Death occurred about forty hours after admission to the hospital. In the patient's room at the hotel was found a bottle of 100 cc. capacity labeled "Ammonium rhodanatum, 100 gm.," still containing a few crystals. These were found to be ammonium sulphocyanate; the blood and extracts from the organs of the cadaver gave strong reactions for the presence of sulphocyanate. The necropsy was otherwise negative.

Therapeutic Use. The first fruitful suggestions for the therapeutic use of sulphocyanates were presented by Pauli in 1903. In his studies of the bearings of the principles of physical chemistry in medicine he found that of a series of common anions the sulphocyanate ion exerts the maximum inhibitory effect on the precipitation of protein, next to it being iodin and bromin ions. From this he concluded that sulphocyanates should exert therapeutic powers comparable in potency with those of iodids and bromids. He reports the results of treatment of 35 clinical cases with 1 gm. of sodium sulphocyanate daily. He found the treatment to exert a very satisfactory sedative action on the pains, vertigo, restlessness, insomnia, irritability, fears, palpitation, increased reflexes, tremors and so forth of neurasthenic conditions, cardiac neuroses, climacteric neuroses (congestions), tabetic pains, syphilitic headaches and similar conditions. In another class of cases exhibiting arterial hypertension Pauli obtained marked reduction of blood pressure, with relief of vertigo and other subjective symptoms. He noted various analogies between the action of iodids and sulphocyanate, even to the occurrence of sulphocyanate acne and rhinitis. Among other things, he notes the use of iodids to promote the elimination of earthy salts, and suggests that the beneficial action of the iodids and sulphocyanates in arteriosclerosis may be due to their power to remove calcareous deposits in the arteries.

A number of other observers following Pauli reported favorable results from the use of sulphocyanate in the pains of tabes, migraine, neuroses, angina pectoris and similar disorders in doses ranging from ½ to 3 gm. daily, the larger doses being found necessary to produce the results in some cases.

In this country Le Roy and Bently (1908–1909) claimed that the sulphocyanates exert a solvent and eliminative action on the earthy salts, which action might be counteracted by excess of ammonia. On this basis they advocated the therapeutic use of sulphocyanates for the removal and elimination of calcareous and similar deposits in various degenerative conditions. This theory of the action of

sulphocyanate is perhaps significant in connection with the use of the related substances, thiosinamin and fibrolysin, for removing fibrous overgrowths. They advocated small dosage, 1 grain four times a day. Le Roy claimed remarkably favorable results—"surprising success" and "all but miraculous good effects," to use his own words—from the use of sodium sulphocyanate in brain and nervous diseases, arteriosclerosis, cretinism, rickets, calcareous deposits about the teeth, cataract, chronic venereal conditions, senility and similar degenerative disorders. Concerning its action in arteriosclerosis, which he attributed to elimination of deposited lime salts, he said: "No remedy can or will reduce the blood pressure so kindly or quickly, when given after a proper manner, as the thiocyanates."

For upward of fourteen years, since having my attention directed to Pauli's work by Dr. Philip S. Roy, I have used sodium sulphocyanate in the treatment of arterial hypertension with the most satisfactory results. The response of blood pressure to this or other treatment depends on the pathology and etiology of the particular case. The arterial factors concerned in hypertension fall into two categories: (*a*) Organic changes in the arterial walls; (*b*) spasmodic contraction of the arterial muscle from nervous, toxic or other influences; either or both of these factors may be present and operative in given cases, resulting in decrease of the volume of the intra-arterial cavity and (other factors being equal) consequent increase of the blood pressure. The total range between the maximum and minimum systolic blood pressures clinically observed in any case of arterial hypertension or sclerosis may be regarded as a measure of the spasmodic element in that case, any residue being of organic origin. Little or no reduction of blood pressure can be expected in the cases where the increase is due to organic change; but the spasmodic hypertension should be quite amenable to treatment. It is without doubt advisable that even nonorganic hypertension should be brought down and kept as low as possible, in order to lessen imposition of a load on the heart that might in the long run tend to weaken the myocardium. It is in this class of cases that sodium sulphocyanate will be most effective; cases with obvious or marked renal or other changes are much less amenable to this or any other similar kind of treatment.

I have found sodium sulphocyanate superior in efficacy for the reduction of blood pressure in appropriate cases to any other medicament, and I believe it to be the best drug in use for that purpose. I use it as a routine, supplanting the iodid of potassium previously so used. Frequently a marked reduction of blood pressure, 20, 30, 40 mm. or more, occurs after a very few doses; in other cases the decline is more gradual. I usually continue administration of the drug for several weeks in order to maintain a lowered arterial tension; and in protracted cases institute a course of the treatment whenever the blood pressure rises unduly, or give it

intermittently, say a week or two in each month. A large proportion of the cases yield very satisfactorily to the treatment.

I have not made any special trial of sodium sulphocyanate as a sedative and eliminant in the various conditions for which it has been recommended by Pauli, Le Roy and others, and am not therefore qualified to express an opinion as to its efficacy along those lines. However, I have not incidentally found the sulphocyanate to exert any marked sedative effects. Further observation will be necessary to develop the full therapeutic possibilities of the drug. Pauli hit upon the therapeutic use of sulphocyanate because in the series of anions considered by him it had the maximum inhibitory effect on the precipitation of protein; if the same reasoning were applied to the basic radicles the ammonium (or possibly the magnesium) salt of sulphocyanic acid might be found even more efficacious than the sulphocyanate of sodium.

I have used sodium sulphocyanate in doses of 5 grains (1 teaspoonful of an 8 per cent solution in water) three times a day, well diluted, after meals, amounting to 1 gram daily. The addition of 1 or 2 drops of phenol would help to prevent the growth of fungi; the addition of peppermint, cinnamon or similar aromatic may lessen nausea. The dose may be reduced to $\frac{1}{2}$ or $\frac{1}{4}$ teaspoonful if the development of disagreeable symptoms necessitates, or as the blood pressure decreases. On account of uncertainty as to chemical or physiologic incompatibilities I have not combined the drug with other medicaments, except for the concomitant administration of nitroglycerin.

A considerable proportion of the patients experience disagreeable effects from the use of sodium sulphocyanate, sometimes so marked as to necessitate reduction of the dosage or discontinuance of the drug. The symptoms mostly complained of are nausea and gastrointestinal disorder; also nervous disturbances. These symptoms may not appear until the drug has been taken for some time, possibly suggestive of an accumulation of it in the system. With a view to obviating the disagreeable results, Nerking introduced for therapeutic use a protein compound of sulphocyanic acid, to which he gave the name "rhodalzid," which he claimed was therapeutically efficient and devoid of unpleasant effects. Pauli claimed to have observed acne and rhinitis produced by sulphocyanate; I have not met with any such effects. Le Roy claimed that patients might suffer toxic symptoms if they ate onions while taking sulphocyanate; I have tried this, but with negative results.

The fact that sulphocyanate occurs close to iodid and bromid in Pauli's series does not seem to me to necessarily indicate that its properties must therefore closely resemble those of the latter substances. Iodids and bromids occur next to each other in that series; yet their properties are quite different.

As illustrative of the therapeutic action of the drug, the following notes from a few cases selected at random are presented:

Case Reports. Case I.—Mrs. F. F., aged about seventy-five years, presented the evidences of senility, arterial atheroma and hypertension, painful arteriosclerotic ulcer of toe, intermittent claudication, mortui digiti, arthritic pains. The blood pressure on February 11, 1924, was 200 systolic and 95 diastolic; after taking sodium sulphocynate the pressure on February 22 was 155 systolic and 85 diastolic; on March 22, 155 systolic and 75 diastolic.

Case II.—Mrs. S. S., aged about sixty-five years, showed obesity, goiter, history of albuminuria and cylindruria and intermittent heart. On June 10, 1922, the blood pressure was 202 systolic and 120 diastolic; after taking sodium sulphocyanate, on July 5 the systolic blood pressure was 140. On April 22, 1924, she reported recent marked epistaxis and vertigo; the blood pressure was 240 systolic and 125 diastolic; she was put on sodium sulphocyanate and nitroglycerin. On May 24 the blood pressure was 180 systolic and 100 diastolic; some vertigo continued and there was mortuus digitus. On June 24 the blood pressure was 165 systolic and 90 diastolic; the symptoms were absent and the urine normal.

Case III.—Mrs. N. C., aged about sixty-five years, on March 22, 1924, gave a history of hypertension, asthenia and arthritic pains; the urine was normal; the blood pressure was 195 systolic and 115 diastolic; sodium sulphocyanate was ordered. On March 27 she developed herpes zoster; the blood pressure was 174 systolic and 110 diastolic. On April 16 the systolic blood pressure was 150.

Case IV.—Mrs. W. B., aged fifty years, during 1919–1920 had several attacks of cholelithiasis; at that time the blood pressure was 110 systolic and 80 diastolic. On May 24, 1920, the blood pressure was 175 systolic and 95 diastolic; after taking sodium sulphocyanate the blood pressure on May 28 was 140 systolic and 86 diastolic. Cholecystectomy was done on June 7, 1920. On August 6, 1920, the blood pressure was 170 systolic and 90 diastolic; after sodium sulphocyanate, 150 systolic and 90 diastolic on September 12. On March 19, 1925, she reported recent biliary colic; the blood pressure was 200 systolic and 100 diastolic; after sodium sulphocyanate, 130 systolic and 80 diastolic on March 25, and 150 systolic and 90 diastolic on April 29.

Case V.—Miss S. C., aged about seventy years, on June 1, 1923, complained of vertigo; the blood pressure was 208 systolic and 102 diastolic. On June 13 the blood pressure was 140 systolic and 90 diastolic. After taking sodium sulphocyanate, on January 18, 1924, she complained of palpitation; the blood pressure was 226 systolic and 110 diastolic; after sodium sulphocyanate the pressure was 125 systolic and 75 diastolic on January 24, and the urine was normal.

CASE VI.—Mrs. W. B., born about 1860, was treated continuously for increased blood pressure from 1913 to April, 1925, when she died from lobar pneumonia. She also had obesity, slight goiter, systolic aortic murmur, recurring arthritis, asthenia; in 1922, after a visit to Panama, she had a nephritic outbreak, with unusual increase of blood pressure, cylindruria (no albuminuria), increase of blood urea, edema of the lower extremities, mental confusion and depression. During the twelve years when she was under constant observation the blood pressure ranged mostly from about 200 to 150. Whenever the arterial tension reached the higher figures sodium sulphocyanate was administered, generally with satisfactory results, although at times the action was somewhat uncertain; however, there was no tendency to increase of the blood pressure range, which at the end of the twelve years' observation was no higher than at the beginning. Disagreeable results attributed to the drug were occasionally manifested, such as loss of appetite, gastric upset, "nervousness," "sense of detachment," quivering and tremor, uncertainty of vision.

CASE VII.—Mr. W. B., a lawyer, aged fifty-six years, had a history of headaches, gastric disturbance, vertigo, tachycardia, intermittent cylindruria, moderate hypertension; he was "nervous" and apprehensive. The blood pressure was 190 systolic and 110 diastolic; after taking sodium sulphocyanate it was 160 systolic and 100 diastolic fifteen days later.

CASE VIII.—Mr. A. C., lawyer, aged sixty-seven years, had cardiac disease, manifested by systolic aortic murmur, arrhythmia, anginoid attacks; he also showed mental confusion and psychotic periods; the urine was normal. His blood pressure ranged mostly from about 200 to 140; there were occasional periods of hypertension, which seemed to be favorably influenced by sodium sulphocyanate. For instance, on July 23, 1924, the blood pressure was 198 systolic and 118 diastolic; on August 5, after taking sodium sulphocyanate and nitroglycerin, his pressure was 150 systolic and 90 diastolic. He had a severe anginoid attack on April 23, 1925, with a blood pressure of 250 systolic and 120 diastolic; he was given sodium sulphocyanate and nitrites, and the blood pressure on April 29 was 180 systolic and 95 diastolic.

CASE IX.—Mrs. A. J. C., aged sixty-eight years, had indigestion, a tendency to myocarditis, hypertension, a systolic aortic murmur and bronchitic asthma; the urine was normal. A large ovarian cyst was removed on August 6, 1924. The attacks of hypertension subsided after sodium sulphocyanate and potassium iodide were given. The blood pressure on January 19, 1922, was 195; after the use of potassium iodid and sodium bromid the pressure

was 165 on February 1. On March 17, 1923, her blood pressure was 198 systolic and 100 diastolic; on April 5, after sodium sulphocyanate was taken the pressure was 175 systolic and 95 diastolic. On April 14, 1925, the blood pressure was 205 systolic and 110 diastolic; on April 19 after sodium sulphocyanate was taken the pressure was 150 systolic and 100 diastolic.

CASE X.—Mrs. S. F. R., aged sixty years, gave a history of hypertension, up to 220; the urine was normal; she had a fibroid uterus and ovarian cyst. Sodium sulphocyanate was given when the blood pressure was elevated, followed by satisfactory reduction; for instance, the blood pressure on November 26, 1923, was 205 systolic and 120 diastolic; on December 1, 185 systolic and 115 diastolic; on December 18, 154 systolic and 90 diastolic.

CASE XI.—Mrs. J. R. H., aged seventy-eight years, showed evidences of senility, indigestion, hypertension, systolic aortic and mitral murmurs, cardiac arrhythmia, bradycardia, attacks of Stokes-Adams syndrome and mental confusion. The urine was negative. The blood pressure on January 4, 1921, was 240 systolic and 85 diastolic, and the pulse was 40; on January 11, after taking sodium sulphocyanate, the pressure was 190 systolic and 70 diastolic. On January 6, 1922, the pressure was 230 systolic and 90 diastolic; on January 10, after taking sodium sulphocyanate, the pressure was 195 systolic and 65 diastolic. On April 20, 1922, she had a Stokes-Adams attack with mental confusion and mania, with a blood pressure of 250 systolic and 90 diastolic; no result was obtained from sodium sulphocyanate, and the patient died on May 3.

CASE XII.—Mrs. F. S., aged thirty-five years, had hypertension (around 250) and nephritis following two pregnancies with eclampsia; the urine was of low specific gravity, with casts and much albumin. The blood pressure ranged from 200 to 270. In this and similar cases with interstitial nephritis no especial reduction of blood pressure followed the use of sodium sulphocyanate.

The therapeutic effect of sodium sulphocyanate in lowering blood pressure is scarcely explainable on the basis of its physiologic and pharmacologic action in large doses as thus far elucidated. In animal experimentation large doses have been found to exert a directly opposite action. Nor does this therapeutic effect seem explainable on the ground of promoting the elimination of calcareous deposits in the sclerosed arteries, since the removal of such deposits would probably take place much too slowly to account for the prompt reduction of blood pressure that frequently occurs. Besides, a more permanent reduction of blood pressure should be

expected from decalcification of the arteries than occurs clinically. Lacking any other explanation, the reference of the sulphocyanates to the indefinite and empirical class of alteratives is rather a confession of ignorance.

Summary. The alkaline sulphocyanates are stable, distinctive, and biologically active substances, entirely different in their pharmacologic properties from the deadly prussic acid and cyanid group. In sufficient amounts they exert potent and distinctive pharmacologic properties, acting especially as intense spinal irritants, with lethal termination. Upward of 15 gm. might cause death in man. For therapeutic use sodium sulphocyanate in doses of up to 1 gram daily (5 grains three times a day) has been found markedly effective in reducing arterial hypertension.

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ABDOMINAL PAIN DUE TO EPIGASTRIC HERNIA.

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Epigastric hernia is quite frequently the cause of vague abdominal pain which is referred to the right upper quadrant and the condition is occasionally diagnosed as cholecystitis, gastric or duodenal ulcer, or appendicitis. If the diagnosis is not made, an exploratory laparotomy is sometimes performed. It is not uncommon for patients who have had a thorough physical examination, gastro-intestinal roentgen rays, Wassermann and urine analysis, all of which are negative with persistence of the original symptoms, to present themselves to hospital clinics when upon careful inspection and palpation of the linea alba, there is revealed a small lump in the midline which is the cause of the abdominal discomfort.

Historical. The first operation for epigastric hernia apparently was performed by Ferrier in 1885 and he insisted upon the hernia being the etiological factor in causing vague upper abdominal pains. The ratio of epigastric hernia to other forms of hernia is put as low as 0.5 per cent and as high as 5 per cent. Imfeld, from Kocher's clinic, reported 450 consecutive hernia cases with 21 epigastric hernias, or 4.6 per cent. In this clinic in the past four years we have had 300 hernias including 4 epigastric hernias or a percentage of 1.33.

Anatomical. If one recalls the anatomy of the upper abdomen, the etiology of epigastric hernia is readily understood. Fig. 1 shows the recti muscles are wider above the umbilicus than they are below. Also the width of the linea alba is greater in the upper part of the abdomen. Fig. 2 shows the linea alba is formed by the interlacing of the anterior and posterior sheaths of the recti muscles. Fig. 3 shows the superior and deep epigastric arteries which are branches of the internal mammary and the external iliac, running in the sheath of the rectus muscles, and not perforating the transversalis fascia. Fig. 4 shows the vessels of the falciform ligament in a large scale, perforating the transversalis fascia and linea alba. The falciform ligament is attached to the anterior abdominal wall just to the right of the midline. In operating on epigastric hernia, one usually finds a tab of fat accompanied by a small bloodvessel which has come from the falciform ligament of the liver. The perforation of the transversalis fascia and linea alba causes a potential point of weakness and through this escapes the properitoneal fat which gradually enlarges and in so doing causes tension on the peritoneum and later a definite peritoneal sac.

Causation. The hernia is usually found in the midline between the ensiform and the umbilicus, approximately 2½ to 3 inches above the umbilicus. There is generally found a small lump which can be reduced by applying pressure over same. This lump is usually

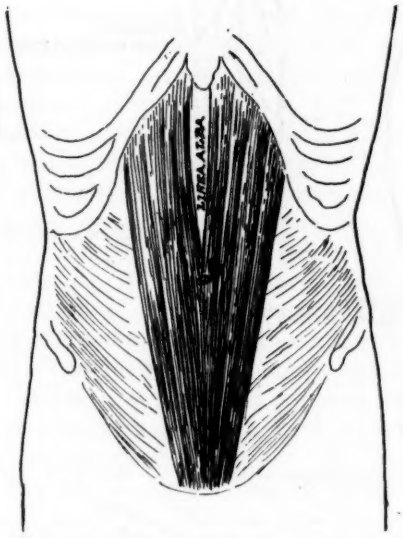

FIG. 1.—Showing space between the recti muscles.

tender to pressure and may not be detected if the patient is prone but is almost always detected if the patient is standing erect, which should be borne in mind when a patient is suspected of having epigastric hernia. Epigastric hernias have been divided into two forms, Quain,[1] (1) Peritoneal lipoma or properitoneal tumor, without

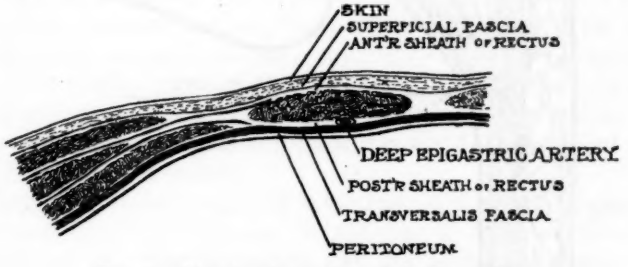

FIG. 2.—Showing formation of the linea alba.

a definite sac; (2) true hernia with the sac of peritoneum with or without contents. Moschcowitz,[2] who does not believe that there is ever a distinct sac present, reports[3] a case of strangulated hernia which contained omentum which required resection. It would seem

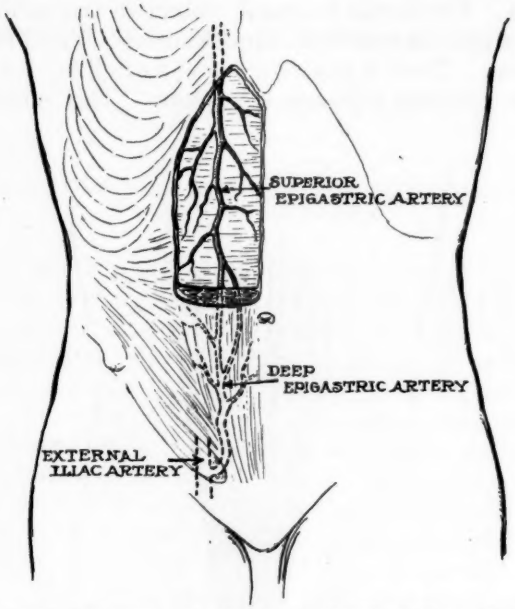

FIG. 3.—Showing epigastric arteries in the sheath of the rectus muscles.

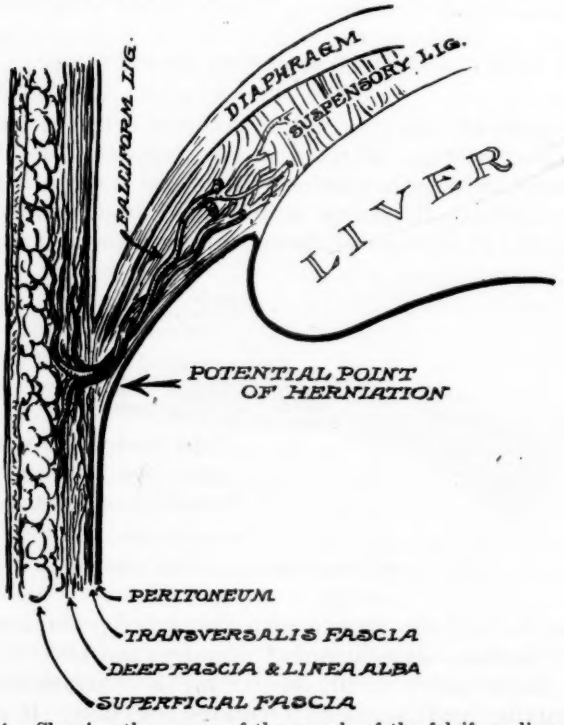

FIG. 4.—Showing the course of the vessels of the falciform ligament.

that the type of hernia encountered will depend on the duration of the history, and the peritoneal lipomata of Quain are only the first stages in producing a definite peritoneal sac, as several strangulated hernias have been reported which contained omentum and intestine. The potential point of weakness in the transversalis fascia and linea alba which have been perforated by the vessels of the falciform ligament allows the peritoneal fat to escape, which gradually enlarges from the intra-abdominal pressure and in so doing produces a definite peritoneal sac.

Signs and Symptoms. Signs and symptoms are rather vague and the case may present symptoms of any upper abdominal condition. It was formerly thought that the gastric distress was due to the fact that the stomach was caught in the herniation, but this does not seem to be true and the pain is usually referred to the biliary tract or the stomach because it is transmitted through the falciform ligament by the tension on the peritoneum. The patients present themselves complaining of pain and discomfort which is usually worse after meals. The distended stomach seems to be the cause of the discomfort. The kind of food does not bear any relation to the discomfort and the patient does not have a periodicity that is encountered in gastric or duodenal ulcer. The pain is worse while standing or bending and is quite frequently relieved if the patient is placed in a prone position. The erect position causes a pinching of the hernial contents by tension of the linea alba which immediately causes a referred pain to the right upper quadrant, through the peritoneal tension. These cases should have a thorough physical examination with gastrointestinal roentgen ray series, Wassermann and urine analysis before the pain is definitely attributed to the hernia. If the hernia is reduced the patient is usually free from pain and discomfort, but as soon as it reappears the discomfort returns. Lewisohn[4] advocates exploratory laparotomies in all cases of epigastric hernia, due to the fact that lesions of the stomach, duodenum or biliary tract are frequently overlooked. This should not hold true if the case has been carefully examined before operation. A herniation the size of a pea is usually the one that is the cause of the symptoms and this is the one that is more often overlooked. The larger hernias are usually easily diagnosed and rarely cause abdominal discomfort.

Treatment. Surgery seems indicated as soon as the diagnosis of epigastric hernia has been made and the abdominal discomfort attributed to it. The operation can be performed under local anesthesia and the transverse incision, similar to the one employed in the Mayo operation for the umbilical hernia may be used. A mass of properitoneal fat which is accompanied by a small blood-vessel is usually found. Whether a definite peritoneal sac is found or not will depend on the duration of the hernia. If there is a definite sac, it may or may not have intra-abdominal contents in

same. If it does, omentum is usually found, but occasionally small intestine or even large intestine is encountered. If a sac does not exist a simple removal of the peritoneal lipoma is all that is necessary, but if a definite sac is present it may be treated the same as an umbilical sac. The linea alba is closed with interrupted chromic sutures. The follow-up of these cases is most satisfactory, providing the patient has been carefully examined before the operation is advised.

Conclusions. 1. The linea alba should be carefully examined in all cases of upper abdominal pain.

2. No case of epigastric hernia should be operated on until all possible sources of abdominal pain are eliminated.

3. Abdominal exploration does not seem indicated in cases of epigastric hernia.

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REVIEWS.

PROTEINS AND THE THEORY OF COLLOIDAL BEHAVIOR. By JACQUES LOEB, late Member of the Rockefeller Institute for Medical Research. Second edition. Pp. 380. New York: McGraw-Hill Book Company, 1924.

THIS posthumous work, containing as it does the conclusions of the last experiments of the author and his associates, constitutes a crowning achievement of a career devoted to lifting the veil of obscurity from so-called vital phenomena. Although the researches of the closing years of his life were a departure from his earlier interest in mechanistic physiology, the author displayed in his work a mastery of logical planning, careful experimentation and critical interpretation that will cause it to stand out as classic. Loeb has sifted the chaotic material on the colloidal behavior of proteins through the screen of classical chemical laws, with the aid of measurements of hydrogen-ion concentration, hitherto neglected because of inadequate methods, and the Donnan theory of membrane equilibria. These efforts in crystallizing a colloidal subject will leave their imprint on the future advance, not only of physical chemistry, but of physiology as well. B. O.

ANAPHYLAXIS AND SENSITIZATION. By R. CRANSTON LOW, M.D., F.R.C.P., Lecturer on Diseases of the Skin, Edinburgh University and Assistant Physician for Diseases of the Skin, The Royal Infirmary, Edinburgh. Pp. 384; 23 illustrations. New York: William Wood & Co., 1925. Price, $6.50.

THIS volume is a presentation of the subject, with special reference to the skin and its diseases. A reproduction of the thesis presented for the M. B. degree at the University of Edinburgh, where it was awarded the gold medal. The work represents both a review of the literature in this field as well as the presentation of some original work by the author. After introductory chapters on the theories of anaphylaxis and the manifestations of anaphylaxis in man, the various forms of cutaneous sensitization are taken up, including urticaria, drug eruptions, the erythemata, sensitization in

tuberculosis and syphilis, dermatitis venenata, sensitiveness of the skin to light and sensitization and immunity to fungus infection. On the latter subject the author has done some creditable investigative work. The book should find favor with immunologists as well as dermatologists. The illustrations in color are very well done.

R. K.

LECTURES ON DYSPEPSIA. By ROBERT HUTCHISON, M.D., F.R.C.P., Physician to the London Hospital and to the Hospital for Sick Children. Pp. 176; no illustrations. London: Edward Arnold & Co., 1925.

THE thirteen lectures making up this book cover the important organic and functional disturbances of the gastrointestinal tract from the author's personal point of view, which is a very rational one, and are intended for the general practitioner rather than the specialist. Brevity has necessitated many dogmatic statements, but the clearness of the diction, the apt quotations and the striking similes employed are most convincing and give to the presentation a charm which is lacking in the usual textbook. Anyone taking it up will read it through and will want to refer to it again. The final chapter on the chronic abdomen is very fascinating.

T. M.

THE BLOOD: A GUIDE TO ITS EXAMINATION AND TO THE DIAGNOSIS AND TREATMENT OF ITS DISEASES. By G. LOVELL GULLAND, C.M.G., M.D., F.R.C.P.E., Professor of Medicine and Clinical Medicine in the University of Edinburgh, President of the Royal College of Physicians of Edinburgh, and ALEXANDER GOODALL, M.D., F.R.C.P.E., Assistant Physician to the Royal Infirmary. Third edition. Pp. 424; 45 illustrations. New York: E. B. Treat & Co., 1925. Price, $7.50.

IN the eleven years that have elapsed since the appearance of the second edition of this work, the temporary stop imposed by the World War to the flood of hematologic literature has allowed a certain number of appraisals to be made. Much valuable new work, however, has also appeared, and the authors take a characteristically conservative point of view toward such of it as remains unconfirmed. The same viewpoint apparently, or possibly a lack of desire to revise thoroughly, has maintained a number of procedures, which in this country at least are no longer used, and has caused the omission of what many consider desirable improvements. In fact it occasionally seems possible to detect certain sections that have obviously been brought up to date to the comparative neglect

of their neighbors. There is also a noticeably small number of foreign references (more than half are British); whether from an overzealous nationalism or lack of acquaintance with foreign literature, the results are equally regrettable. On the other hand, the book is well balanced, systematic and no grave omissions of first importance are noted. One would like to see presentations of the dynamic balance of blood formation and destruction, Sabin's recent studies on blood cell formation, the movements of leukocytes and so on. Removal of the section on the mechanism of blood clotting from the description of hemophilia to its proper position would improve matters. Although perhaps one of the best books on the subject in English, it emphasizes the need in our language for some such book as Ferrata's *Emopatie* or Pappenheim's *Grundriss der haematologischen Diagnostik*. E. K.

ENZYME INTELLIGENCE AND WHENCE AND WHITHER. By NELS QUEVLI, Reg. Phar., LL.B. Pp. 578; 83 illustrations. Minneapolis: The Colwell Press, Inc., 1925. Price, $3.65.

"ILLUSTRATING that enzymes and ferments are the ultimate, indestructible and invisible units of life and are conscious and intelligent. That these units produce and maintain all living things we see. That our body is a republic established by enzymes coming from the invisible world of life to which we return when we die." Further comment is unnecessary. E. K.

PROCEEDINGS OF THE THIRD INTERNATIONAL CONGRESS OF THE HISTORY OF MEDICINE AT LONDON, 1922. Pp. 320; illustrated. Antwerp: de Vliit, 1923.

THIS volume presents those papers read at the London Congress which have not appeared in other publications. The fifty-three items make up a considerably smaller presentation than the proceedings of the second Congress at Paris, but as it contains no record of the titles published elsewhere, a comparison of the scientific production of the two congresses is impossible. From all other points of view, however, the volume is inferior to its predecessor. It is to be hoped that the published proceedings of the fifth Congress, recently held in Geneva, will return to the previous high standard. A number of papers are grouped around the set topics of mediæval epidemics, and the history of anatomy; the majority are disconnected varia, among which many will doubtless be found to interest those historically inclined. E. K.

A COMPEND OF DISEASES OF THE SKIN. By JAY FRANK SCHAMBERG, Professor of Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania. Seventh edition. Pp. 316; 110 illustrations. Philadelphia: P. Blakiston's Son & Co., 1925.

THIS well-known little book fulfills all the requirements of a publication of its scope. The recent advances in therapeutics, such as foreign proteins, actinotherapy and chemotherapy are set forth in clear and sufficient terms. The ever-changing therapy of syphilis is brought down to date. Such adverse criticisms as might be offered are minor ones; thus, it might be better if blastomycosis were transferred (page 302) from the category of new growths to that of the inflammatory diseases. The book deserves the continued patronage which a seventh edition indicates.

F. W.

1924 COLLECTED PAPERS OF THE MAYO CLINIC AND THE MAYO FOUNDATION. Vol. XVI. Edited by Mrs. M. H. Mellish. Pp. 1331; 254 illustrations. Philadelphia and London: W. B. Saunders Company, 1925. Price, $13.00.

THE present volume follows the previous policy of this well-known clinic in forming a complete reference record of all papers for the year, whether given in full, abridged, abstracted or by title. More than two hundred titles by one hundred and sixty authors are sufficient indication of the quantity of research work work turned out there annually. In quality, as one would expect, there is considerable variation. First-class articles, usually by the senior members, are interspersed with some of lesser merit and with abstracts that are so short that they serve for little more than to carry out the aforementioned policy. All readers, however, should find something suitable for their palates, and to those liking their mental pabulum in large single doses such a volume will be preferable to a periodical journal, as it undoubtedly is to many of them in substance.

E. K.

A COMPEND OF OBSTETRICS. Especially Adapted to the Use of Medical Students and Physicians. Revised and edited by CLIFFORD B. LULL, M.D., Instructor in Obstetrics, Jefferson Medical College, Assistant Obstetrician to the Maternity Department, Jefferson Medical College Hospital, etc. Tenth edition. Pp. 272; 84 illustrations. Philadelphia: P. Blakiston's Son & Co., 1925.

THIS book is intended for use as an aid to rapid review by those preparing for examinations. It will be found to be complete, concise, well arranged and has been thoroughly revised.

P. W.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Primary Vascular Nephritis, or Renal Periarteritis Nodosa.—Periarteritis nodosa is of such rarity, only seventy cases having been recorded in literature, that the recognition of the disease antemortem is exceptional. Clinically the disease may be recognized by the following clinical picture, according to KEEGAN (*Arch. Int. Med.*, 1925, **36**, 189). There is an acute or gradual onset of obscure sepsis with emaciation, weakness, prostration, fast pulse, marked leukocytosis and frequently intermittent abdominal pain. The arteries most frequently involved are the coronary and the smaller vessels of the kidney. An affected artery shows well-marked nodules with frequent small aneurysms or thrombotic obstruction and infarction. In addition to the interest aroused by the very full case report of an unusual disease, particularly of moment in the author's study, is the fact that the right kidney was removed at operation some weeks prior to the death of the patient and a wonderful opportunity was presented to contrast the early and late pathologic picture of the condition, together with the effect the disorder had upon the kidney itself. The acute lesions of the first kidney were found to be changed in the second into early arteriosclerosis. The intima was greatly thickened by young white fibrous tissue, leading to anemia of the cortex, with atrophy, fibrosis and infarction. The cortex was narrowed and the tubules markedly atrophied with a varying degree of replacement interstitial fibrosis. When the patient was first seen there was but scanty evidence of renal insufficiency. Subsequently cardiac decompensation, decreased

urinary output, nitrogen retention and a terminal uremia developed, undoubtedly the result of the rapid arterial obliteration. The pathology in this case naturally suggests to the author the possibility of a certain number of cases of chronic vascular nephritis being caused by a mild nonfatal attack of renal periarteritis nodosa. The term, chronic vascular nephritis, ordinarily is applied to the arteriosclerotic kidney of the aged, a condition characterized by extension of the sclerosis of the aorta and large vessels into the renal artery, by an absence of the clinical symptoms of kidney disease and by a cardiovascular death. The combination form of Volhard and Fahr, while primarily vascular in origin, is characterized by extensive glomerular change and the development of the signs of renal insufficiency, often ending in uremia, while cardiac compensation is adequate. If the author's conception of the origin of the vascular changes in an acute arteritis holds true it would fully explain the difficulty of the experimental reproduction of the glomerular type of vascular nephritis, because the organism causing periarteritis nodosa is extremely difficult to isolate, and probably is highly adapted to the human environment.

Pathogenicity of Trichomonas Intestinalis.—There is considerable difference of opinion among parisitologists as to the pathogenicity of Trichomonas intestinalis. The majority consider these flagellates to be harmless, but to a well-informed minority they seem to be apparently entirely capable of producing definite symptoms and pathology. TSUCHIYA (*Arch. Int. Med.*, 1925, **36**, 174) undertook a reinvestigation of the subject from the clinical and laboratory point of view. He found that in a series of 30 cases there were no urinary metabolic, blood, gastrointestinal, nervous, nutritional or circulatory symptoms which could be attributed to the trichomonas infestation. Diarrhea, presumed by many to be the result of trichomonasis, was present in only two of his cases. Furthermore, he noted that the type of intestinal flora does not alter the number of trichomona.

Diseases of the Liver: I. A Survey of the Tests for Hepatic Function; II. A Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice.—These two papers, the first by GREENE, SNELL and WALTERS (*Arch. Int. Med.*, 1925, **36**, 248), the second by the first two authors in collaboration with ROWNTREE (*loc. cit.*, p. 273), present obvious difficulties in abstracting, but will well repay those interested in liver functional tests who read them in the original. The authors give a most excellent summary of previous work done by others and show in experimental obstructive jaundice, among other findings that the van den Bergh test affords a simple and accurate means of studying the degree of bile retention and the progress of icterus, and that the phenoltetrachlorphthalein test shows dye retention in the blood stream that closely parallels the degree of bile retention.

Ketogenic Diet for Epilepsy.—Going on the assumption that the ketone bodies developed in the body during the imperfect burning of fats might possess the same sedative action on the central nervous system as do the anesthetics, PETERMAN (*Jour. Am. Med. Assn.*, 1925,

84, 1979) made use of a high fat diet for epilepsy with apparently remarkable results. Limiting the protein to 1 gm. per kilo body weight and the carbohydrate to 10 to 15 gm. daily, he made up the remainder of a high caloric diet with fat. Such a diet he usually found to produce acetone bodies in the urine in a few days. In cases where it failed to do so he found that the administration of 20 to 25 gr. of sodium bicarbonate, in addition to the diet, brought about this desired end. The success of such dietary treatment of epilepsy in children appears striking from a survey of the author's data. Of 37 patients treated, 19 have been entirely free from attacks for periods ranging from three months to two and a half years. Several patients have had attacks only following breaks in the diet, usually carbohydrate indulgence. Thirteen patients were definitely improved and 12 of these are still undergoing dietary adjustment to further control the convulsions. Three were free from convulsions for three to eight months and were then lost sight of. One made no improvement and 1 is still early in treatment. In some cases the high fat diet is not well tolerated by the patient, especially if started too abruptly. The nausea and vomiting sometimes occurring at the start are readily relieved by orange juice. Carbohydrate must be avoided so far as possible, however, because it is just this lack of glucose oxidation that brings on the desired ketosis.

SURGERY

UNDER THE CHARGE OF

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Polyposis of the Colon.—ERDMANN and MORRIS (*Surg., Gyn. and Obst.*, 1925, **40**, 460) state that the term polyposis of the colon is used to designate an adenomatous hyperplasia of the intestinal mucous membrane as opposed to those polypoid tumors of the intestines which are histologically fibromata, myomata, etc. Polyposis of the colon appears to be a uniform, nonspecific mucous membrane reaction to a chronic irritant in the presence of a preternaturally sensitive mucous membrane. It is manifested grossly as scattered intralumenary tumors, varying in size from a split pea to a grape-fruit and has a specific predilection for the large gut and rectum. This predilection increases as we proceed from the ileocecal valve. Two clinical types may be distinguished—an adolescent variety in early youth with recurring attacks of intestinal hemorrhage and diarrhea and showing a distinct tendency to involve members of the same family, and an acquired variety first appearing in

adult life in association with frank evidences of chronic traumatic and inflammatory lesions to which they are evidently secondary. The two types have in common the marked predilection for the large gut, a malignancy incidence of more than 40 per cent and a tendency to chronic intestinal hemorrhage and diarrhea. They are dissimilar in that the adolescent type is widely disseminated, appears in almost countless numbers and shows no gross evidence of a causative lesion, while the adult type occurs in limited number and is almost invariably associated with gross evidence of trauma, inflammation or foreign body. Indications for treatment are the depleting hemorrhage, diarrhea and the high malignancy incidence. Nonradical palliative treatment comprises cecostomy, irrigations and radium therapy. Radical effective treatment, excision of the polyp-bearing area is limited by technical difficulties and the inability to predict preoperatively the extent of the process.

Tannic Acid in Treatment of Burns.—DAVIDSON (*Surg., Gynec. and Obst.*, 1925, **41**, 202) states that the preliminary treatment of burns with tannic acid compresses followed by exposure to air lessens toxemia. After coagulation of the devitalized tissue with tannic acid the application of a wet boric acid dressing apparently causes a return of toxic symptoms. Tannic acid as an initial dressing on a burn is analgesic. The subsequent use of the open air method causes minimal trauma and promotes general comfort. The local astringent effect prevents the loss of body fluid. Secondary infection is markedly limited by the absence of a favorable nidus for bacterial growth. Scar tissue formation has been less marked than that observed after treatment by other methods. The protective layer of coagulated protein forms a scaffold for the growth of the young epithelial cells over the denuded surface.

Cystic Inflammation of the Vesical Neck and of the Prostatic Urethra.—LAZURUS (*Surg., Gynec. and Obst.*, 1925, **41**, 162) claims that cysts and polypi around the internal vesical sphincter and in the prostatic urethra are frequently secondary to specific and nonspecific prostatitis. Such cysts and polypi can attain very large dimensions and be mistaken for neoplasms. The lesions in this condition differ from those in cystitis cystica in that they never invade the bladder and are of a purely inflammatory nature. A combination of fulguration of the cysts and of local treatment for the prostatic condition will always yield excellent results in these cases.

The Residual Paralysis and Deformity of Anterior Poliomyelitis.—MITCHELL (*Jour. Bone and Joint Surg.*, 1925, **7**, 619) says that anterior poliomyelitis is an infectious disease characterized by inflammation of the gray substance of the spinal cord and attended by motor paralysis and deformity. It is of wide distribution and often occurs in epidemics. Experiments have shown that the infecting organisms enter the body probably through the upper respiratory passages. In this series the disease occurred during the first three years of life in 44 per cent of the patients. The onset is acute, but the residual state of deformity is permanent and may progress or become accentuated by

the growth of the child. Usually the patient does not seek aid until after the deformity has become well established. The average duration of the paralysis in a series of 350 cases was eight and three-fourths years. The paralysis is most marked in the lower extremities. The anterior tibial muscle was the one most commonly paralyzed. Talipes equinus and talipes vulgus were the most common deformities. Scoliosis occurred in 31.4 per cent of the cases. Marked improvement follows proper treatment given early in the disease. The treatment consists of rest, massage, the applications of heat, muscle training and the use of splints and braces. In many cases surgical treatment of the residual deformity is of great benefit. It aids in correcting deformities, stabilizing the limb and increasing the function of the limb.

Abnormal Arteriovenous Communications, Acquired and Congenital.—REID (*Arch. Surg.*, 1925, **11**, 25) says that an arteriovenous fistula is a powerful stimulus to the development of a collateral circulation, much greater even than is the stimulus of ligating the vessels. A fistula between artery and vein leads to marked changes in the vessels. The arteries proximal to the fistula become dilated and thin-walled and often show marked degenerative changes. A true aneurysm may form in an artery proximal to the fistula. The veins dilate and their walls may become thickened. A fistula between large vessels may lead to grave cardiac disturbances or even to sudden death. The circulation of a limb distal to a fistula is usually markedly impaired, even though there is an increase in the capillary bed. The surface temperature distal to a fistula is lowered, while after extirpation of the fistula it may be several degrees higher than it is normally. Arteriovenous or cirsoid aneurysms situated in the extremity of a growing individual may cause a considerable increase in the length of that extremity. In the author's experiments a kidney does not live after a complete reversal of its circulation.

Perinephritic Abscess in Children.—PUGH (*Urol. and Cutan. Rev.*, 1925, **7**, 387) writes that perinephritic abscess, particularly that due to metastases is more common than generally supposed. The history of an infection and pain in the costovertebral angle in children should arouse suspicion. All cases are not so clear cut as those in this series and should be given the benefit of a complete urologic examination if possible. An exploratory operation is justifiable in doubt. Surgery in this class of cases can and should be done under local anesthesia. Experience has convinced the authors of the great prevalence of urological manifestations in children and the field opened by modern technics.

A Basis for Comparing Results in the Treatment of Ureteral Calculi.—HAHN (*Am. Jour. Surg.*, 1925, **39**, 161) states that cystoscopic findings were positive in 97 per cent of the cases. These positive findings in order of frequency are as follows: Diminished excretion of indigocarmine by one kidney, partial obstruction of ureter, complete obstruction of ureter, scratch mark on wax-tipped bougie, no excretion of indigocarmine by one kidney, stone seen at ureteral orifice, stone seen in bladder, ecchymosis and edema near ureteral orifice and

grating sound or sensation upon passing ureteral catheter. In 4 cystoscopically negative cases there were positive roentgenograms, and in 2 red blood cells in the urine previous to cystoscopy. The roentgen ray misses 17 per cent of ureteral stones. In a series of 147 cases positively diagnosed as ureteral stones 17 per cent of the stones were passed spontaneously before cystoscopy; 15 per cent of the stones were passed at or following cystoscopy; 37 per cent of the stones required operative removal; 30 per cent of the patients were treated conservatively. Of the cases in which the stone was not passed spontaneously, and could not be induced to pass by a reasonable trial of cystoscopic methods, 55 per cent required operative removal.

Periarterial Sympathectomy.—BERNHEIM (*Surg., Gynec. and Obst.*, 1925, **40**, 828) states that the socalled periarterial sympathectomy of Leriche is a procedure that may be of great usefulness in the prevention and relief of circulatory disorders of the extremities that are wont to eventuate in gangrene. The operation consists essentially in the elimination of sympathetic nerve control over certain bloodvessels, as a result of which they are permitted to dilate and carry apparently a greater quantity of blood than they had been carrying. Exact indications for its use remain somewhat problematical but certain states characterized by a spastic condition of the bloodvessels offers its greatest field. Nothing is to be hoped for in arteries completely thrombosed, and at the present time the arteriosclerotic disorders, diabetic and syphilitic, do not seem amenable to relief in this manner. The operation itself, while not simple or devoid of danger is not too difficult and any surgeon of experience should be able to do it satisfactorily. The chief point of importance is to secure absolute removal of the adventitial coat of the artery, since the sympathetic nerve fibers are for the most part in this coat and the purpose of the operation is their removal.

Tuberculosis of the Tongue.—FINNEY and FINNEY (*Surg., Gynec. and Obst.*, 1925, **40**, 743) claim that there were only 2 cases in women among 15 cases. Direct trauma seems to be the only important causative factor in any of these cases. In no case was the trauma to be charged to that popular bugbear, the pipestem. Pain is not a prominent feature in this list of cases. In only 1 case was pain of the excruciating character usually described. There is no site of predilection for the development of the lesion. Any portion of the tongue may be attacked with most of the lesions occurring anterior to the circumvallate papillæ and about equally divided between tip, margins and dorsum. The tongue lesions may be single or multiple. There may or not be any regional adenopathy. The authors have no special form of treatment to advocate. It would seem wise, however, in a case which seems to be primary to treat it by wide excision, much as if it were carcinoma.

Preoperative Skin Disinfectant.—SCOTT and HILL (*Jour. Urol.*, 1925, **14**, 135) state that the alcohol-acetone-aqueous solution of mercurochrome which is made by dissolving 2 gm. of mercurochrome in 35 cc. of distilled water, and then adding 55 cc. of 95 per cent alcohol and 10 cc. of acetone, is a very efficient preoperative skin disinfectant.

Better skin sterilization is obtained with it than with iodin, "kalmerid" and picric acid. Its application is accompanied by no pain, and it is therefore of special value in cases operated upon under local anesthesia. Regardless of the age of the patient or location of the operative field, no instances of dermatitis have occurred following its use in the authors' series. This solution penetrates at least as deeply as picric acid and seems to be a little more uniformly distributed at its lower level of penetration. It retains high bactericidal properties at least for forty-six days, as shown by controlled experiments upon a rabbit skin heavily inoculated with Staphylococcus aureus. It has a relatively low toxicity, as shown by the vigorous way that tissue cultures and transplants have grown after its use.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Control of Rickets.—ELIOT (*Jour. Am. Med. Assn.*, 1925, **85**, 656) remarks on the extraordinary chronicity of rickets in his series of roentgenograms. The evidence of rickets first seen in the second or third month of life may be followed month after month even to the end of the first year or later. If the infant is under treatment evidence of lime salt deposit as well as the evidence of active rickets may be seen. The process finally becomes low grade and sluggish, and though constantly present is controlled. If the infant is not under treatment the roentgenogram shows increasing and accumulating evidence of the disease month after month, until the well-known picture of marked rickets is seen. Lime salts apparently can be deposited in one part of the cartilage of a growing bone, when they are not deposited in other parts. Rickets and the repair of the rachitic process go on hand in hand for months, and in some instances for years. That rickets is intimately associated with growth is well known, and that it should appear at the time when most active growth is taking place, namely, the first four months of life, is not extraordinary. Large, rapidly growing breast-fed babies and very fat infants uniformly show definite evidence of rickets. It is an uncommon thing to find a healthy vigorous baby although breast fed who does not show rickets by roentgen-ray examination. Premature babies who grow exceedingly rapidly are notoriously rachitic. Malnourished infants frequently show small, slender bones with little or no rachitic change. If any two groups of infants show need of early antirachitic treatment more than the others they are the large, rapidly growing breast-fed infants and premature infants. The investigations showed that a slight degree of early rickets is almost universal in our climate and in our state of society. The very intimate association of rickets with growth, its

early appearance regardless of season and its universality engenders the question, whether this slight degree of rickets must be considered normal. The author is not prepared to answer this question at this time. Before an answer can be accurately arrived at it would be necessary to study the amount of rickets existing in a group of infants born and living in the tropics.

Static Peritonitis in Malnourished Infants.—FOOTE (*Jour. Am. Med. Assn.*, 1925, **85**, 720) says that premature, toxic and typically athreptic infants display symptoms of peritoneal injury in a manner that may be termed static. One of these patients showed infection through the umbilical vein. In intussusception in the athreptic infant pain, tumor and vomiting may only be seen late in the disease, and diagnosis may be difficult. Even slight distention, not reducible by enemas in emaciated infants, should be contraindicated for intraperitoneal instillation of salt solution or of blood. A gain in weight after this procedure in desperately-ill athreptic patients means a nonabsorbing peritoneum. Usually by the time that it is possible to establish the diagnosis with certainty treatment is unavailing. Hence the need for prophylaxis of athrepsia by breast-milk feeding and care as to the hygiene of the infants in the first weeks of life. The use of pituitary extract to promote peristalsis in young infants is fraught with danger, since it readily produces intussusception. In defining the hypothreptic infant, Marfan speaks of those infants who have not passed the threshold of actual atrophy, and he describes as athreptic those who show the characteristic syndrome. This syndrome is ordinarily caused by food injuries plus acute infections, such as pharyngitis. Chronic or subacute infections, such as tuberculosis, syphilis, or the terminal stage of such acute infections as are produced by the less virulent types of the dysentery group of bacteria, may also be the provoking agents of the metabolic disturbance. The apparent functional disability of alimentation, as shown by defective digestion and absorption, has in the past been attributed to the impaired nutrition of the intestinal glands and of the intestinal mucosa and the muscularis.

Does Roentgen Ray Modify the Course of Whooping Cough?—FABER and STRUBLE (*Jour. Am. Med. Assn.*, 1925, **85**, 815) report the results of a study based upon equal numbers of control and test cases, selected in such a manner as to afford if possible a just comparison between those treated and those not treated with the roentgen ray. Forty-four consecutive cases in the paroxysmal stage of pertussis formed the material for this study. Twenty-two of these were given treatment by roentgen ray and the remaining 22 were treated with antipyrin. With 5 exceptions, the division of patients into the two groups was by alternation. Of the 5 exceptions, 2 patients were suffering from a rather severe form of the disease, their inclusion has raised the average number of paroxysms and perhaps the average duration of the disease in the irradiated group. It may have been better not to have treated the control group at all, or perhaps with a placebo. This was not done, as it did not seem right to leave the children untreated, so moderate doses of antipyrin were given. The irradiated patients were also given the same drug when it was evident that no effect was being

obtained from the roentgen ray. The two groups, therefore, afford a comparison between children treated with antipyrin and children treated with roentgen ray plus antipyrin in some cases. The diagnosis was made on characteristic symptoms, and in most instances was corroborated by blood count. Cultures were not taken. Mothers were required to make daily notation of the number of paroxysms, which were defined as a coughing spell followed by a definite whoop, and of vomiting attacks. These reports were brought to the clinic once a week. After the disappearance of the whoop reports were continued for some time. Delinquents were followed. The roentgen-ray treatments were uniform, according to the following specifications: Eight milliampères, 9-inch parallel spark, 0.25-mm. copper and 1-mm. aluminum filters, 12-inch anode skin distance to 6-inch circular areas front and back of the chest. Treatments were graduated by age periods, and were given on the first fourth and eighth days of observation. These observers found that the disease ran an average longer course, fewer patients ceased whooping in the early weeks and more patients were whooping in the later weeks in the irradiated series than in the controls. This study would appear to justify the conclusion that roentgenotherapy is without true beneficial effect in pertussis. The method used here did not differ in essentials from that used by others. It may be that occasional temporary exacerbations or inhibitions may occur shortly after roentgen-ray treatment, but these should probably be ascribed to psychic disturbances. Effects of greater extent or duration, such as have been previously reported from roentgen ray, as from other modes of treatment, are in all probability apparent rather than real, and represent normal fluctuations in the course of a highly variable disease.

Universalizing Breast Feeding in a Community.—RICHARDSON (*Jour. Am. Med. Assn.*, 1925, **85**, 668) gives the three essentials for accomplishing this procedure: (1) There must be a group of physicians who are convinced of the overwhelming superiority of breast feeding over bottle feeding, who believe that it is attainable for the vast majority of infants, and who are familiar with a working technic for making breast feeding possible for the individual child; it is well known that the main points of this technic are the manual expression of the mother's breasts after nursing and the giving of complimentary feedings whenever the amount of breast milk secreted is insufficient, the amount taken to be judged from the desire of the infant. (2) There must be coöperation of the birth-recording department or bureau of the community. (3) There must be an organization controlling sufficient nurses trained in the technic of breast feeding visit each new mother as soon as a birth certificate is filed, in order to instruct her in the desirability of keeping the baby on the breast, as well as in the way to accomplish this. They found that nine-tenths of the mothers succeeded in nursing their babies for one month, and that two-thirds of them did so for seven months. The infant mortality rate of the 2815 babies studied was 49 per 1000. That of the county for the year of the campaign was 64. The mortality rate for the three previous years averaged 72. The morbidity of children nine months breast fed, as compared with that of children less than nine months breast

fed, was said to effect, as would be supposed, diseases of the digestive tract, where the ratio was almost 3 to 1 in favor of breast feeding. Respiratory diseases showed the next highest variation. Pneumonia and bronchitis was very prevalent in the children with limited breast feeding. These children were also susceptible to infectious diseases, especially whooping cough, measles and chicken pox. One-third of the children prematurely weaned became sick as over against one-eighth of those who were breast fed for nine months.

GYNECOLOGY

UNDER THE CHARGE OF
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Bilateral Urethral Implantation.—The subject of ureteral implantation must be of interest to every gynecologist, since there are occasions, either accidental or intentional, when it is necessary to perform such a procedure, and only when such an operation is performed by a perfected technic can favorable results be expected. For many years this subject has been investigated by COFFEY (*Northwest Med.*, 1925, **24**, 211) who has recently made another contribution in this field. Being interested in the radical cure of carcinoma of the bladder and in the relief of inoperable carcinoma, he realized that diversion of the kidney function was the first essential to success in either case. He discovered experimentally that both ureters could not be transplanted at the same time, for the reason that there seemed to be a postoperative edema in the intestinal wall which was sufficient to obstruct the lumen of the ureter and thus temporarily destroy kidney function. Animals in which both ureters were transplanted died. When one ureter was transplanted the urine would not come into the intestine for from three to eight days and then the kidney would begin to function in a normal way, and it has been found necessary to permit the first kidney to have sufficient time to recover its function before the second ureter is transplanted. Removal of the bladder then meant a third operation. Patients of the cancer age usually have a diminished kidney function and diminished resistance in other respects, therefore the ordeal of three operations have seemed so formidable that few have had the temerity to use it in cancer. Another drawback has been that the ureters are frequently dilated from back pressure when the patient comes to the surgeon. The improved technic which he is now using consists of opening the abdomen near the median line. A rectal tube is passed up into the pelvic colon to a point where it is desirable to implant the left ureter. This

tube drains away all gas and any possible fecal matter which may be present and makes the use of clamps unnecessary. The left ureter is exposed and ligated between forceps. The distal end is cauterized with carbolic acid and dropped back. Into the proximal end is fastened a very small rubber tube, 2 or more feet in length. This is done by passing a small straight needle armed with linen through the wall of the ureter and including barely enough of the tube to hold. Then the thread is tied around both the tube and ureter sufficiently tight to control the urine and later to cause sloughing of the tied end. The right ureter is then treated in the same manner. It will be found that the urine is discharging through both of these tubes. Next the intestine on the left side is lifted at a point where the ureter may be inserted without tension or strain. Gauze is packed on either side of the intestine so that any possible leakage from the intestine will be caught. An incision about 1½ inches long is made near the center of the free margin of the largest intestine and made to curve over to the outer side. This incision goes through the peritoneum and muscle, and the mucosa is carefully freed from the muscularis, allowing the mucosa to pouch out through the incision in the muscular wall. The same is performed lower down the intestine on the right side. A small stab wound is made through the mucosa at the lower angle of the intestinal wound and the end of the small rubber tube is attached by a linen suture to the end of the rectal tube. On the right side a small incision is made in the mucosa and the end of the right ureteral tube is attached to the side of the rectal tube. A nurse then pulls down on the rectal tube and draws the two ureteral tubes down until the ends of the ureters are drawn well within the lumen of the intestine. The ureters containing the tubes now lie directly on and outside of the loose mucosa of the intestine. The wall of the intestine on either side of the cut, forming the two lips of the wound, is drawn across the ureter and some of the sutures are made to penetrate the outer coat of the ureter. These sutures should be of interrupted chromic catgut. Finally a continuous catgut suture should roll the serous coat over the line of incision, thus reinforcing it, and the abdomen is then closed. The tubes protruding from the rectum are placed in a container for the urine. The kidneys function without even temporary cessation. The tubes come away in about a week, the swelling in the intestinal wall has subsided and the implantation is complete. By the use of the tube to transmit the urine through the edematous tissues surrounding the anastomosis, the kidney functions just as if the ureter were brought out through a loin wound, therefore both ureters may be implanted simultaneously with impunity, and it may even be possible to remove the bladder at the same sitting, but, as a rule, this had better be deferred until a later time.

Autotransfusion in Ruptured Tubal Pregnancy.—In the tragic type of ruptured tubal pregnancy the successful outcome of surgical operation often depends on the quick replacement of the blood lost. This is usually accomplished by means of blood transfusion, but very often valuable time is lost in securing a donor of the proper type. In order to overcome this difficulty, autotransfusion, or recovery of the blood in the peritoneal cavity and reinjecting it into the patient's vein, has

been suggested as a valuable procedure, and a report on the use of this method in 26 patients has been presented by HEMPEL (*Zentralbl. f. Gynäk.*, 1925, **49**, 407). Of this series there was 1 death of a patient who was moribund and who died on the table. The author begins the operation by giving an intravenous infusion of normal saline solution. After the solution is flowing freely in the vein the abdominal incision is made. A small midline incision is made and the peritoneal edges are drawn upward so that very little of the blood in the peritoneal cavity can escape through the incision. The contained blood is scooped out of the peritoneal cavity, strained and mixed with sodium citrate solution and then placed in the container which holds the saline solution, which should be kept warm throughout the procedure. The abdominal incision is then enlarged and the remaining blood is scooped out, obtaining as much as possible by changing the position of the table and by milking the blood from the flanks. As quickly as possible, without losing too much blood, the diseased tube is clamped and removed. The condition of the patient is usually so much improved by means of the transfusion that the remainder of the operation proceeds in an orderly fashion with little danger. By means of this autotransfusion it is often possible to return to the patient's circulation from 1000 to 2000 cc. or more of blood. Whereas formerly it was obligatory to perform these operations in fifteen minutes, by means of this technic the patient is usually able to withstand careful removal of both tubes if advisable and even appendectomy. Since ectopic pregnancy recurs in from 5 to 9 per cent of cases, Hempel believes it is advisable to remove the opposite tube if the patient has children and is not anxious to have more.

The Cancer Problem.—As on several previous occasions, it is again our privilege to call attention to some of the conclusions of HOFFMAN (*Pub. Health Jour.*, 1925, **16**, 256), one of our best-known cancer statisticians, which have been reached as a result of his recent survey in San Francisco. His investigation concerning living cancer patients clearly proves that there has been on an average a loss in weight of about 30 pounds between the onset and the termination of the disease. General indications are that most of the patients, while in good health, were above the average weight in proportion to their height. Many of them frankly admit themselves to be heavy eaters, particularly heavy meat eaters and heavy sugar eaters, while only a small proportion of the patients were heavy fat eaters. In about one-half of the cases there is an admission of a chronic condition of intestinal stasis and of the habitual use of purgatives or laxatives. In about one-third of the cases the patients suffer, or have suffered, from rheumatism or a chronic rheumatic condition. The evidence regarding heredity was practically negative. The argument frequently proposed that many of the cancer patients of large cities are nonresidents is clearly disproven by the San Francisco investigation. The average duration of residence had been twenty-two years in San Francisco and thirty-three years in California. The sum and substance of the problem may be summed up in the statement that the principal cause of cancer mortality is delay on the part of the patient to seek qualified treatment. The appalling mortality from cancer admits that a cure for the disease, in

the technical sense of the term, has not been discovered, but it would be unfair to the medical and surgical profession, states the author, if attention were not drawn, to an increasing extent, to successful forms of control, but for which the cancer death toll would reach, even ordinarily, more alarming proportions. Anyone familiary with hospital or private medical and surgical experience knows full well that thousands and tens of thousands of persons who have been operated on for cancer are alive and well today. It is regrettable that the collective experience in this respect should not have long since been brought together as an unanswerable argument of the dictum that in the earliest qualified treatment lies the only hope of cure.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Psychic Manifestations in Cases of Brain Tumors.—MOERSCH (*Am. Jour. Psychiat.*, 1925, **81**, 705) found that of 239 cases of brain tumor at the Mayo Clinic 73 had definite mental changes. A high percentage of unilateral frontal or corpus callosum tumors showed such changes. All callosal tumors were in this group. The author groups the psychic symptoms of brain tumors under three headings: (1) General symptoms, such as mild mental and physical let down (neurasthenic states); mild changes in personality (indifference, inadequacy, "witzelsucht"); anxiety states; depressive reactions; mental confusion; deteriorating states simulating epilepsy, arteriosclerosis, senile dementia, vascular lesions, traumatic lesions, dementia paralytica, dementia precox (catatonic states); these have no localizing value according to the author. (2) Specific mental reactions, such as lack of effect (change in personality); impaired mental grasp (lack of memory, interest and attention); impaired insight and judgment; impaired mental activity (poverty of thought processes); disturbances of general motility (psychosomatic); in the absence of localizing signs these constitute what the author calls a frontal lobe syndrome, meaning that it is not positive, but suggestive. (3) Associated mental reactions, such as hysterical episodes, maniacal states, or other psychotic states which may be quite independent of the effects of the neoplasm and are usually seen in neuropathic individuals. Seven tumor case histories are given to illustrate symptoms and lesions in various parts of the brain.

A Review of Some Studies of Delinquents and Delinquency.—HEALY (*Arch. Neurol. and Psychiat.*, 1925, **14**, 25) reviews 4000 cases of delinquency in children of average age, fourteen to fifteen years, half of whom were in Boston and half in Chicago. Over development, especially in girls, seemed to be the rule. Premature puberty occurred

in 10 per cent, delayed puberty in 3 per cent. Sensory defects were not unusual in frequency. The most common organic nervous disease was chorea. The author feels that the whole group has a greater incidence of head traumata than the normal. Congenital syphilis was relatively rare. The socalled stigmata of degeneration were present in 6 per cent. Goiter was many times more frequent in the Chicago group. Definite feeble mindedness was present in 13.5 per cent of the total group. More of the Chicago group had psychoses (5.6 per cent to 1.1 per cent). Epilepsy was present in 5.5 per cent of the Chicago group and in 1.8 per cent of the Boston group. The author cites the result of 127 mentally abnormal boys who were in need of special care but did not receive it. Ninety-three of them committed desperate acts and were the source of great expense to the state.

Extensive Brain Hemorrhage.—WINKELMAN and ECKEL (*Jour. Nerv. and Ment. Dis.*, 1925, **61**, 593) report briefly 30 cases of cerebral hemorrhage. In 22 the hemorrhage had broken into the ventricles, and in these cases death occurred from five hours to fifteen days after onset. Convulsions occurred in only 2 cases. Consciousness was lost soon after the onset in 23 of the 30 and was altered in 4 others. One case of hemorrhage into the pons was fatal in an hour. The authors conclude that cerebral hemorrhage and even pontine hemorrhage is not a cause of immediate death.

Mental Examinations of College Men.—PECK (*Am. Jour. Psychiat.*, 1925, **4**, 605), in a review of 59 students at Harvard considered 22 normal, 14 had minor personality defects, 20 were neurotic and 3 psychotic. They were classified roughly according to Jung's classification of extraversion and introversion. Extraverts predominated. Case histories are given illustrating both introverts and extraverts, with varying degrees of personality defect. The writer feels that there is a very definite need for psychiatric examinations among college men as a prophylactic and therapeutic measure.

The Relation of Intelligence to the Etiology of Drug Addiction.—KOLB (*Am. Jour. Psychiat.*, 1925, **5**, 163) cited two surveys (Boston and New York) from which it was concluded that more drug addicts are mentally deficient than is found in normal social groups. In the writer's group of 100, composed of colored and white, and in which he did not place some higher grade professional individuals who were addicted, there were 10 with intelligence quotient below 70; 10 with intelligence quotient between 70 and 75; 14 between 76 and 85; 38 between 86 and 95; 20 between 96 and 105; 7 between 106 and 110; 1 over 110. There were 25 colored people included in this group. The writer feels that the Stanford-Binet test is not a fair measure for adults. The basis of drug addiction is thought to be a neurotic or psychopathic personality which is only indirectly related to any defect of intelligence.

Negative Histologic Findings in Experimental Organic Processes.—ORTON (*Am. Jour., Psychiat.*, 1925, **4**, 599) states that death was induced in experimental animals by methods which obviously impli-

cate the central nervous system. In the first group of 5 animals both carotid arteries were suddenly ligated and 3 of them promptly had convulsions. In the second group of 8 dogs tetany parathyreopriva was induced, and the animals were killed in various stages of the disease. In the third group animals died in convulsions from acute oxalic acid poisoning. In the fourth group animals were allowed to develop convulsions from an overdose of insulin, or were caused to have convulsions from moderate doses of insulin over a period of time. In all groups careful histologic studies were made of the brain. Some variations in histologic structure were observed, but nothing was found which could not occasionally be seen in the controls. The writer justly concludes that if no constant structural changes can be demonstrated in animals that died obvious cerebral deaths, we are far from being able to ignore the organic possibilities of some of the psychoses, even though no pathologic variations are demonstrated.

Epidemic Encephalitis.—The various methods of treatment of this disease are mentioned and referred to in the bibliography. STRECKER and WILLEY (*Am. Jour. Psychiat.*, 1925, **4**, 631) treated 14 patients with sequels of encephalitis by intravenous injection of 10 cc. of 0.5 per cent neutral acriflavin. The average time from the onset of the disease until treatment was begun was three years and four months. They report marked improvement in 3 cases; some improvement in 7 others; very little or no improvement in 4. A table is given showing the condition of patients before and after treatment. In 2 cases pregnancy went to term with delivery of healthy children while the patients suffered from the sequels. In 2 other cases the onset of the disease was soon after childbirth. The authors are hopeful that this method of treatment may be as helpful in other cases as in their own.

The Use of Lipiodol in Tumor of the Spinal Cord. — MIXTER (*Arch. Neurol. and Psychiat.*, 1925, **14**, 35) reports the results of lipiodol injection for the diagnosis of cord tumors in 12 cases. When injected into the lumbar sac, and the patient placed in the Trendelenberg position, the oil gravitated poorly toward the head. A meningeal reaction reached its height in twenty-four to forty-eight hours following the injections. In some cases the cell count reached 1000 and the fluid even became slightly turbid at the height of the reaction. Lipiodol apparently has remained unchanged in the spinal canal eight months after injection. The appearance of an oily cap in the roentgenograms in the region of a suspected tumor seemed to be confirmatory evidence. The author cites the work of the French and brings up the criticism that lipiodol may not be of value in cases of tumor without block. As with all diagnostic procedures, lipiodol should not be relied on solely, but should assist where physical diagnosis has been carefully done.

Aseptic Meningitis in the Treatment of Dementia Precox.—CARROLL, BARR, BARRY and MATZKE (*Am. Jour. Psychiat.*, 1925, **4**, 673) state that it has been known for years that some cases of dementia precox improve temporarily while reacting to an acute infection or inflammatory process. Following other lines of research, especially on

aseptic methods of producing irritation in the spinal canal, Carroll injected 25 cc. of inactivated horse serum into the spinal canal of a patient in a catatonic stupor. An aseptic meningitis followed, but no mental change. The same treatment was given a week later, and the following day the patient "was quite himself for the first time since admission." Of 49 cases so treated at the Philadelphia Hospital for Mental Diseases 14 showed no improvement, 28 were improved and 7 showed remissions. A detailed account of laboratory examination of cells of spinal fluid is given. Contraindications for continuation of this treatment are failure of temperature to return to normal, or an eosinophilia of 15 per cent or more. A large number of case histories detail in a fragmentary way the status of patients before and after treatments. Within two to eleven months after producing aseptic meningitis the authors draw conclusions as to the therapeutic effect of this method of treatment. In other ways the study seems inadequately controlled.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Fibroma of the Acoustic Nerve.—It is known that certain tumors, such as glioma, dural endothelioma and the acoustic nerve fibroma may develop at the cerebellopontile angle. CUSHING (*Tumors of the Nervus Acusticus*, Saunders, 1917) called attention to the acoustic nerve tumor as a clinical and pathologic entity, their origin usually being in the sheath of the eighth cranial nerve. Most of these neoplasms are unilateral. When bilateral they are usually an expression of a widespread affection of nerve sheaths commonly known as von Recklinghausen's disease. Clinically, the acoustic tumors, owing to the characteristic chronology of their symptoms, may, as a rule, be sharply distinguished from all other tumors of the cerebellopontile angle. According to Cushing, the symptomatic progress of the average acoustic tumors occurs more or less in the following stages: "(1) The auditory and labyrinthine manifestations; (2) the occipito-frontal pains with sub-occipital discomfort; (3) the incoördination and instability of cerebellar origin; (4) the evidences of involvement of adjacent cerebral nerves; (5) the indications of an increase in intracranial tension with a choked disc and its consequences; (6) dysarthria, dysphagia; and finally cerebellary crises and respiratory difficulties." JACOBSON (*Am. Jour. Path.*, 1925, **1**, 259) adds 3 cases of cerebello-pontile angle tumors, which came to his attention at autopsy. All were females, aged forty-six, twenty-two and forty-four years, respectively, the oldest individual having bilateral tumors. Histologically, the four tumors in these 3 cases were almost identical and agreed essentially with the

descriptions of the eighth-nerve tumors as given by Cushing, Mallory, Councilman and Goodpasture. They were fibromas with, however, slight deviation from the staining reactions of fibroblasts in tumors elsewhere. Their origin was apparently from the perineurium of the acoustic nerve, and they had many points of resemblance to peripheral neurofibromata. A regimental or palisade arrangement of nuclei was practically always present in some degree. The so-called reticular tissue, the author concludes, was probably the result of degeneration due to hemorrhage or thrombosis or other vascular injury. He quotes Cushing as giving the incidence of acoustic tumors in 1035 verified brain tumors as 91, or 8.8 per cent.

Abnormal Development of the Nasal Cavity of Dogs Due to Interruption of the Respiratory Curent.—As only one incompletely reported experiment on the influence of the respiratory current on the growth of the nose was found in the literature, CONGDON (*Proc. Soc. Exper. Biol. and Med.*, 1925, **22**, 566) interrupted the respiratory current on the left side of the nose of 11 freshly weaned puppies by introducing cotton through a window out at the dorsal end of the hard palate. The packing was changed daily and the experiment continued in most of the series for forty-six days. In 6 dogs the conchæ showed markedly incomplete development on the operated side, leaving a wide open space adjoining the septum. The usual marked curvature of the conchæ was almost completely lacking. The septum was slightly concave on the operated side, and the frontal sinus on the average was slightly larger. Histologically, no difference on the two sides was demonstrated with certainty. There was no unusual asymmetry of the face. A perfect contrast of the condition as to air circulation on the opposite side was prevented by a pressure atrophy of the septum, allowing the packing to extend somewhat over onto the unoperated side, which may explain the negative outcome in 5 of the animals. The author considered three possible factors in bringing about the arrest of development, namely, infection, stoppage of drainage and the elimination of the physical effects of the air current, chief among which are fluctuations of pressure, temperature and moisture. The evidence, as a whole, pointed to the physical effects of the air current as the cause of the abnormal development.

Studies on Pneumonia following Nasopharyngeal Injections of Oil.—It has long been customary in many children's hospitals, among pediatricians and rhinologists in private practice, to treat nose and throat infections by the use of drops of menthol and albolin or by the use of argyrol drops. This treatment, while not always beneficial, has been regarded as more or less harmless. In the routine study of autopsy material in a large pediatric institution, LAUGHLEN (*Am. Jour. Path.*, 1925, **1**, 407) encountered an unusual microscopic picture in the sections of the lung from a pneumonia case, wherein large vacuolated "oil-containing" mononuclear cells were found in the consolidated portions of the bronchopneumonic process. He was able to collect 5 cases in all—4 in children and 1 in an adult, aged thirty-seven years. Three of the children had received drops of menthol (1 gr.) in albolene (1 oz.) into the nose over varying periods of time. The fourth child

had received, while in a diabetic stupor, 2 drams of paraffine oil by mouth as a laxative, while the adult, who had paralysis of the soft palate, vocal cords and accessory muscles of larynx, had been given 1.5 oz. of liquid paraffine by mouth three times a day over a period of four and one-half months, also as a laxative. In each instance certain portions of the pneumonic exudate showed the peculiar oil-laden endothelial cells. In order to explain the source of the oil and the route by which it reached the pulmonary alveoli, as well as to prove that oil would produce such reaction in the lungs of animals, several experiments were performed on rabbits, administering the menthol-albolene mixture in various ways. It was learned that the oil found its way into the alveoli of the lung, not only when directly introduced into the trachea but also at times when given in sufficient quantity in the nose and throat. In the experiments where oil was administered by mouth as well as in the clinical cases the reactions to oil were complicated by septic pneumonia, but when the oil was injected by needle into the rabbit's trachea a purely endothelial-cell reaction resulted. In the lung the oil was actively phagocyted by endothelial cells, which were present in sufficient numbers to dispose of all the oil present and produce consolidation of the lung. On the other hand, argyrol when given by mouth or introduced into the trachea, did not lead to any reaction on the part of the endothelial phagocytes in the lung.

RETROSPECTOR'S COMMENT: These are very interesting and instructive observations. In the light of these findings should not one consider more seriously not only the promiscuous use of mineral oil in the nose and throat, but also the intratracheal instillation of similar substances?

Studies on Fusiform Bacilli and Spirochetes: Occurrence in Putrid Ethmoiditis.—It has been demonstrated by Davis, Pilot, Pearlman, Brams and others that the fusiform bacillus and the associated spirochetes are important etiologic factors in putrid and necrotic lesions; that in the mouth, where they normally reside, they are responsible for certain types of foul pyorrhea, ulcerative stomatitis and typical Vincent's angina; that like the streptococci and other pyogenic bacteria in the mouth and oropharynx, they may extend into the middle ear and give rise to the fetid discharges in chronic otitis media. More recently PILOT and LEDERER (*Ann. Otol., Rhinol. and Laryngol.*, 1925, **34**, 366) reported the occurrence of these anaërobic microörganisms in 2 patients with putrid ethmoiditis. In 1 case the fusospirillary forms were recovered at autopsy from a thick pus in the ethmoid cells of a female with syphilis. In the second case, a female, aged twenty-six years, the fusiform bacilli and spirochetes were found in the expectorated material and in the ethmoidal pus encountered at operation. After twelve doses of neoarsphenamin the odor, secretion and crusting had entirely disappeared. The striking characteristic of the infection of the ethmoid cells in both instances was the foul character of the pus. In this respect sinus infection with these organisms resembled in their behavior the putrid processes observed about the mouth and in the lungs. In most of these infections the sources of infection are those organisms found normally about teeth, tonsils and in the nasopharynx. In the tartar of teeth they are constantly found. In the

tonsils bacilli occur in 82 per cent and spirochetes are particularly numerous in the granular actinomyces-like masses. In the adenoids the bacilli were observed in 32.6 per cent and spirochetes in 5 per cent. The discharge from typical cases of ozena was examined in several instances, with negative results.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Staphylococci from the Liver, Gall-bladder and Intestine of Normal Dogs.—ARNOLD, BALTHAZAR and DRAGO (*Jour. Infect. Dis.*, 1925, **36**, 413) have studied the bacteria in the cystic bile and mucosa and their relation to the bacteria in the duodenum of healthy dogs. An attempt was also made to classify staphylococci from the liver, cystic mucosa and duodenum of healthy dogs on the basis of fermentation reactions and effect on gelatin, nitrates and milk in order to determine the possible source of gall-bladder strains. A series of 63 apparently healthy dogs was used, the cultures being taken first from the bile in the gall bladder, then from the cystic mucosa, and finally from the duodenum, all with the usual aseptic precautions. Details of the media and technic are given. In 5 of the 63 dogs the bile contained bacteria. In 44 bacteria were demonstrated in the cystic mucosa; 39 of these exhibited sterile bile. Details of the findings are reported. Selected strains from bile and mucosa were passed several times through rabbits. Following this 10 healthy dogs were selected, and the strains of the animal passages were injected, both with and without preliminary injection of Dakin's solution, but nothing remarkable was noted. Eighty-five strains of Staphylococcus albus were studied, recovered from the liver, gall-bladder mucosa, duodenum, mouth and colon of 27 dogs. The findings were indefinite but tended to indicate the strains of Staphylococcus albus recovered from the duodenum, mucosa of the gall bladder and liver were biologically more active than the others and resembled Staphylococcus aureus in character, though only showing white colonies. As a result of the study, the authors concluded that no relation could be determined between the bacteria in the duodenum and those in the cystic mucosa. The Staphylococcus albus isolated from the normal cystic mucosa of dogs was not pathogenic for dogs or rabbits.

Heat Produced by Union of Antigens with Antibodies.—A most interesting study by BAYNE-JONES (*Jour. Immunol.*, 1925, **10**, 663) demonstrated that heat was produced by the union of diphtheria toxin and

antitoxin and also by the agglutination of Bacillus typhosus with its agglutinating serum. There were two periods of heat production in this latter reaction. The first, reaching its apex in one and one-fifth hours, was attributed to the combination of the agglutinin with the bacteria. The second, reaching its peak in five hours, was attributed to the clumping and flocculation of the bacteria and was considered analogous to the evolution of heat by the flocculation of colloids. The determination of the diphtheria toxin-antitoxin reaction was based on the union of 1 unit of diphtheria antitoxin with 1 L_f amount of toxin. This latter unit, 1 L_f, is determined by the Ramon flocculation test and includes all the affinities of the antitoxin. The author used the differential microcalorimeter of Hill and converted, by appropriate apparatus, the temperature changes to microvolts and degrees centigrade. The determinations required most delicate controls and careful measurements.

Allergic Reactions to the Hemolytic Streptococcus.—The association of streptococcus infections with various pathologic lesions remote from the site of the bacterial focus leads to the, at least logical, explanation that an allergic reaction may be responsible for the conditions. ZINSSER and GRINNELL (*Jour. Immunol.*, 1925, **10**, 725) give some experiments evidently supporting this explanation. Guinea pigs could be rendered allergic (intracutaneous injections of 0.1 cc. of the streptococcus material) by the growth of streptococci in agar foci (Dochez), by treatment with streptococcus nucleoprotein (prepared by acid precipitation of antiformin solutions of streptococci), by injection of Dick filtrate, but the most regular and potent method was by the injection of the whole living bacteria. The Dick filtrate was the most potent substance for the demonstration of the reactions by skin test. The authors point out the interesting analogy between streptococcus allergy and the tuberculin reaction in that sensitization is most successful when the whole bacteria are injected and that the Dick filtrate which corresponds in manner of production to an unconcentrated O.T., without glycerin, is the most potent material for the demonstration of the allergic state by skin reaction.

Studies in Group Agglutination: The Absorption of Agglutinin in Diphasic Salmonellas.—Continuing his previous observations that in ordinary cultures of salmonella—Bacillus ærtrycke, Bacillus paratyphosus B and C and the Newport type—the bacilli exist side by side in two forms or phases sharply distinguished by their behavior in agglutination but not in other respects, ANDREWS (*Jour. Path. and Bacteriol.*, 1925, **28**, 345) presents a study of the absorption test in this connection. Six types of salmonella are given careful and thorough consideration. Details are reported of the preparation of bacillary emulsions and sera in pure phase forms necessitating the testing of the agglutination of individual colonies. The proportions of group antigen in the specific phase and of specific antigen in the group phase were determined by absorption. This was, in short, contrasting the absorbing power of the specific and group phases of a given type first upon a pure monospecific and then upon a pure group serum prepared from that type. Details are also given of how the proper dose of each phase was deter-

mined by first plotting normal absorption curves. The "critical" dose, roughly corrected for the original titer of the serum was determined for graded absorptions of the ultraspecific serum, first with the specific and then with the group phase of the organism, and then for for the converse absorptions of the pure group serum with the two phases. Percentage absorption graphs were plotted. An example of the data and procedure are given. It was found that the difference in absorbing power between the two phases is very great. In short, the specific phase possesses more than one hundred times the absorbing power for the specific agglutinin shown by the group phase, while the group phase is more than four hundred times as efficient as the specific phase for the absorption of group agglutinin. A comprehensive discussion of the variations in the results of different strains is followed by a discussion of the structure of the group elements of the salmonellas and suggestions on practical applications. It is shown that the question of phase is not one which can be neglected in absorption work involving diphasic organisms.

The Renal Circulation Rate in Experimental Oxalate Nephritis.—DUNN, DIBLE, JONES and MCSWINEY (*Jour. Path. and Bacteriol.*, 1925, **28**, 233) were prompted by the swollen and anemic appearance of the kidney in nephritis to investigate the rates of bloodflow, comparing the nephritis with the normal organs. Their method of measurement of rate of flow was to draw off the whole of the blood from a renal vein during a measured period of time by means of a syringe and needle, the animals' circulation being left otherwise intact. A marked disadvantage was the lowering of the blood pressure by the anesthetic. A description of the experiments and details of the technic are given. Nephritis was induced by intravenous injection of sodium oxalate into rabbits. Ten normal and ten nephritic animals were used. Blood-urea determinations are reported in the nephritic animals, and in some of the normal. It was found that there was a greater mean circulation through the kidneys in rabbits suffering from oxalate nephritis with urea retention than in normal animals.

Further Indirect Evidence that Anaërobes Tend to Produce Peroxid in the Presence of Oxygen.—M'LEOD and GORDON (*Jour. Path. and Bacteriol.*, 1925, **28**, 147) publish a report of further work on the biologic activities of anaërobes. Pneumococcus has been shown to be a producer of H_2O_2. This organism produces a greenish discoloration in heated blood ("chocolate") agar. The anaërobes under investigation likewise produce this change, and this is the basis for the presumption that they produce H_2O_2. A survey of earlier work and observations is followed by a report of the effects of the addition to the media of various reagents likely to react to H_2O_2. Bacillus tetani was the organism chiefly investigated, and pneumococcus was used as a control. Catalase from unheated blood and from liver extract, delayed or inhibited the green discoloration. The best results were obtained using catalase from unheated blood. Sensitivity to sulphids may have retarded the action of catalase in Bacillus tetani cultures. Small amounts of manganese dioxid, which could safely be added to the medium, were found to have little effect. The addition of glutathione

(a dipeptid made up of cystin and glutamic acid) which is a thermostable nitroprussid reacting substance appears to promote both growth and green discoloration. These findings are further evidence in support of H_2O_2 production by anaërobes. An excellent plate illustrates this paper.

HYGIENE AND PUBLIC HEALTH

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Recent Researches in Cancer.—GYE's researches (*Lancet*, 1925, **211**, 109) have led him to look upon cancer—using the term in its widest sense—as a specific disease caused by a virus (or group of viruses). Under experimental conditions the virus alone is ineffective; a second specific factor, obtained from tumor extracts, ruptures the cell defenses and enables the virus to infect. Under natural conditions continued "irritation" of tissues sets up a state under which infection can occur. The connection between the specific factor of a tumor and an irritant remains to be investigated. Some of the relatively unimportant "irritants" are known, such as coal tar, paraffin oils, etc. The virus probably lives and multiplies in the cell and provokes the cell to continued multiplication. BARNARD (*Lancet*, 1925, **211**, 117) has studied Gye's virus by special microscopic methods, and describes small bodies which may be seen and photographed.

The Epidemiological Importance of Diphtheria Carriers.—In study of 758 clinical cases of diphtheria in Baltimore, DOUL and LARA (*Am. Jour. Hyg.*, 1925, **5**, 508) found that of 2799 family contacts not receiving prophylactic antitoxin 59, or 2.1 per cent, were attacked later than one and not later than thirty days following the onset of the primary case. In contrast to this, investigation has shown that in the family contacts of 1044 school carriers, estimated to number 4665, only 14 cases were reported within thirty days of the discovery of the carrier. After making necessary allowance for differences in age distribution of the two groups of contacts, it is a conservative estimate to state that the risk of attack is ten times as great for family contacts of cases as for those in similar association with known bacillus carriers. Comparison of the attack rates in families of carriers with the prevailing attack rates in the general public of the city indicates that during the first month following discovery of the carrier the attack rate in the family contacts is considerably higher than would be expected in a random sample of the city's population of the same age distribution,

whereas in subsequent months no such excess is indicated. The interpretation of the excess attack rate in carriers' families during the first month of observation is complicated by a number of considerations which are noted in the presentation of the data. Nevertheless, it seems reasonable to conclude, since the statistical observations are in agreement with many other general facts known regarding the epidemiology of diphtheria, that the families of known bacillus carriers do incur a risk of developing clinical diphtheria which, though small, is appreciably higher than that incurred by otherwise comparable families in which such carriers are not known to exist. It should be noted, however, that the evidence cited justifies this conclusion only as regards carriers discovered in schools where clinical diphtheria was prevalent at the time, for among the family contacts of chance carriers, found in a random sample of school population, there is no evidence of any greater incidence of diphtheria than that prevailing in the general population of the city. The number of carriers of this kind observed, namely 104 "virulent" and 261 "avirulent" is, however, too small to justify any sweeping conclusions regarding the risk of attack to which their family contacts are subject. This study fails to show any significant distinction between the risk of attack for those exposed respectively to carriers classified as "virulent," "avirulent" and "not tested." The fact that such are not brought out by analysis of the data presented does not, however, justify the conclusion that differences do not exist, and it may be that a study of a larger number of families would indicate that the risk of attack may vary according to the type of bacillus harbored by the carrier.

Humidity Control in Residences.—DRINKER (*Am. Jour. Pub. Health* 1925, **15**, 689) states that during the months of central heating, increasing the humidity of the air permits the maintenance of lower temperatures, decreases dustiness, prevents the deterioration of plants and furnishings, and improves the atmosphere from the standpoint of health and comfort. The chief drawbacks in humidity control are: (*a*) Loss of moisture, initially through absorption by the contents of the residence, and constantly through air leakage; (*b*) condensation of moisture on cold objects, such as windows; (*c*) increase in fuel consumption. Mechanical humidifiers, such as sprays and centrifugal atomizers are discussed, as well as devices in which moisture is evaporated from pans on radiators, from troughs of warm air furnaces, and from the surface of wet towels or wicks. A mechanical humidifier functioning by the last method is described and illustrated. Typical performance curves are given, showing the evaporative power of these devices in different humidities and the control they effect.

Interracial Variation in Infant Mortality.—DEPORTE (*Am. Jour. Hyg.*, 1925, **5**, 454) states that there has occurred in the six-year period, 1916 to 1921, a definite decline in the rate of infant mortality in all racial groups. The decline has been both absolute and relative, reducing the degree of variation between the rates of the diverse groups. The differences in the rates of infant mortality of the several groups have been due primarily to differences in the rates of mortality from diseases of the digestive and of the respiratory systems, and, therefore,

in large measure, influenced by environmental factors which are, theoretically, preventable. There has been less change, absolute and relative, in the rates of mortality of infants under one month. These deaths are brought about by causes as yet little understood, and except in the cases of premature births not likely at the present time to yield to organized public effort. The differences between the various groups in these rates very probably have a biologic basis, and in this sense may be termed racial.

The Germicidal Properties of Soap.—WALKER (*Jour. Infect. Dis.*, 1925, **37**, 181) claims that soaps are not to be regarded as general germicides, but in using them for their detergent properties advantage may be taken of their germicidal activity against the streptococcus, pneumococcus, diphtheria bacillus and to a lesser extent against the typhoid bacillus. The thorough washing of the hands with the formation of a good lather will destroy any adhering diphtheria bacilli, streptococci and pneumococci. Any ordinary soap will serve for this purpose. Cocoanut oil soap is the only soap appreciably active against the typhoid bacillus at ordinary temperatures. In order to kill typhoid bacilli on the hands the washing should extend over a period of at least three minutes, with the formation of an exceedingly stiff lather. The use of a nail brush in washing the hands in order to render the surface under the nails accessible to the action of soap is desirable. The activity of soap is greatly enhanced by raising the temperature. This germicidal activity of soap against the typhoid bacillus seems to be due to its high content of the saturated fatty acids and the very low proportion of unsaturated acids. Foreign substances interfere markedly with the germicidal activity of soap. It is suggested that linseed oil or cottonseed oil used in the manufacture of the official sapomollis might be advantageously replaced by cocoanut oil. The greater use of cocoanut oil soap would aid in the prevention of the spread of typhoid fever by hand contamination.

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